CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-714

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NICOTINE INHALER

(Nicotine Inhalation System)

NDA 20-714

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

HFD- 170

DATE COMPLETED: Mar. 5,1997

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-714

NICOTINE INHALER

(Nicotine Inhalation System)

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act for 1069(NEPA) as the national charter for protection, restoration and enhancement of the environment. NEPA establishes policy, sets goals (Section 101), and provides procedures (Section 102) for carrying out the policy.

Environmental information is to be available to the public and decision maker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless details.

The Food and Drug Administration Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have significant affect on the quality of the human environment in the United States and an environmental impact statement therefore will not be prepared.

In support of their new drug application, Pharmacia AB has prepared an abbreviated environmental assessment (21 CFR 25.31a (b)(5) which evaluates the potential environmental impacts of the manufacture and use of the product.

Nicotine, which is a naturally occurring substance, is an alkaloid contained in the leaves of the tobacco plants, Nicotiana tabacum and Nicotiana rustica. It will be administered in a plastic tube (cartridge) with a porous plug containing 10 mg of nicotine and a mouthpiece which will be used to hold the cartridge for inhalation of nicotine. The Nicotine Inhaler will be used for the treatment of smoking cessation. The drug product will be manufactured, packaged, and labeled by Pharmacia AB in Helsingborg, Sweden.

Returned or rejected drug product will be disposed of at licensed disposal facilities. For home use, used systems and their packaging components will be disposed of by the patient as household solid waste.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any adverse environmental effects. Precautions taken at the site of manufacture of the bulk product are expected to minimize occupational exposure and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property eligible for listing in the National Register of Historic Places.

Date

Juanita M. Ross 3/5/97
PREPARED BY
Juanita M. Ross
Review Chemist
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170

Date

3/7/97
CONCURRENCE
Albinus D'Sa, Ph.D.
Team Leader
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170

4/7/97
Date

Nancy B. Sager
CONCURRENCE
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Material Safty Data Sheet(drug substance)

FREEDOM OF INFORMATION (FOI)

NON-CONFIDENTIAL

ABBREVIATED ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-714

NICOTINE INHALER

(Nicotine Inhalation System)

10 mg/Unit

TABLE OF CONTENTS

ENVIRONMENTAL ASSESSMENT FOR NICOTINE INHALER, 10 mg/unit

1. DATE

August, 1995

2. NAME OF APPLICANT

Pharmacia Inc

3. ADDRESS OF APPLICANT

Pharmacia Inc
P.O. Box 16529
Columbus, OH 43216, USA

4. DESCRIPTION OF PROPOSED ACTION

4.1 Request for Approval - Need for Action

This Environmental Assessment is being submitted in support of the NDA for Nicotine Inhaler.

The active component of this product is a naturally occuring substance (nicotine). Therefore, this submission has been prepared as an Abridged Environmental Assessment as defined under 21 CFR 25.31a (b) 5. However, as information is available, the report contains some information concerning the environmental fate and effects of the drug ingredients.

Nicotine is an alkaloid contained in the leaves of the tobacco plants *Nicotiana tabacum* and *Nicotiana rustica* (Reinhardt and Britelli, 1981). A tobacco leaf usually has a concentration of 1 - 2 % nicotine. Cigarettes manufactured in the United States contain 8 - 15 mg nicotine and deliver up to 2.5 mg each of nicotine. An average US standard cigarette delivers 0.5 - 0.6 mg of nicotine. Nicotine is also released to the air in the particulate phase of tobacco smoke (Tso, 1969).

The Nicotine Inhaler is proposed as an aid to smoking cessation for the relief of nicotine withdrawal symptoms.

4.2 Locations where product will be formulated into finished form

The Pharmacia facilities, intended for production of Nicotine Inhaler, are situated in an industrial area in the northern parts of the town Helsingborg

in Sweden (Pharmacia AB, P.O. Box 941, S-251 09, Sweden). The active ingredient, nicotine, is delivered in bulk to the above plant.
The Helsingborg facility consists of buildings for pharmaceutical manufacturing, offices and research laboratories. The total area is approximately 55000 m^2. Adjacent property includes a commercial area, a park, and a housing area. The climate is seasonal.

No protected or sensitive environments, endangered or exotic species, or historic archaeological areas are considered to be impacted by the manufacture or use of the Nicotine Inhaler.

The Pharmacia Helsingborg plant holds a licence for pharmaceutical production according to the Swedish Environment Protection Act (Licence 1992-07-08, 2410-15903/91). A Statement from the local environmental authority is attached (Appendix I).

4.3 Location(s) where finished product will be stored, distributed and, when necessary, destroyed

The finished product will initially be stored in a storehouse in the southern parts of Helsingborg, Sweden. The Nicotine Inhaler will then be distributed to the United States.

Nicotine inhalers that have reached their expiration date or are otherwise rejected will be returned to Pharmacia. Returned units will be disposed in accordance with all Federal, State and Local environmental regulations.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES

The active ingredient used in the manufacture of the Nicotine Inhaler is nicotine. Other (inactive) ingredients of the inhaler are ethanol, levomenthol and a porous plug (nitrogen is also used during the manufacturing process).

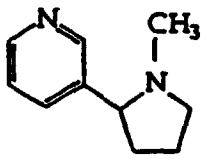
5.1 Active ingredient

5.1.1. NICOTINE

SUBSTANCE IDENTIFICATION, CHEMICAL AND PHYSICAL PROPERTIES

Chemical name:	S-3-(1-methyl-2-pyrrolidinyl)-pyridine, β-pyridyl-α-N-methyl pyrrolidine
CAS Registry Number:	54-11-5
Molecular Formula:	$C_{10}H_{14}N_2$

Structure:



Boiling Point:	247.3 °C
Melting Point:	-79 °C
Molecular weight:	162.23
Log Octanol/Water Partition Coefficient:	1.17 (nicotine base, pH 7)
Water Solubility:	soluble in water
Solubility in Organic Solvents:	soluble e.g. in ethanol and ether
Vapor Pressure:	1 mm Hg (61.8 °C)
Appearance:	colorless to pale yellow oily liquid, turns brown in air or light, hygroscopic, burning taste
Impurities:	cotinine, myosmine, nicotine-N-oxide, β-nicotyrine (any individual ≤0.5%; total ≤1.0%)
TOXICITY DATA	
LD_{50}:	3.3 mg/kg, oral mice; 53 mg/kg, oral rat
EC_{50} Daphnia:	0.242 mg/L, *Daphnia pulex* (Perry and Smith, 1988) 0.326 mg/L, *Daphnia pulex* (17 °C) (Passino and Smith, 1987)
LC_{50} Fish:	no data; concentrations of 3 - 29 ppm of nicotine have been shown to be toxic to fresh water fish (Weiss, 1986)
EC_{50} Algae:	no data available

Other effects: Nicotine is a highly toxic compound that transiently stimulates and then severely depresses the central nervous system. Death can be caused due to respiratory paralysis and a depolarizing block of the nerve muscle junction of skeletal muscle. Chronic effects include a rise in mean aortic blood pressure, elevation of plasma free fatty acids, disturbance in heart rhythm, a rise in metabolic rate, loss of appetite etc (Reinhardt and

Britelli, 1981). Nicotine has been shown to have adverse effects on reproduction, fetal weight gain and development. The chronic effects associated with smoking cigarettes (lung cancer, emphysema, heart disease) are believed to be due to the tars and carbon monoxide present in the smoke.

ENVIRONMENTAL FATE AND EXPOSURE POTENTIAL

Natural Sources: Nicotine is obtained from the stems and leaves of tobacco plants *Nicotiana tabacum* and *Nicotiana rustica* where it occurs in concentrations of 1 to 14 percent, usually 1 to 2 percent (Reinardt and Britelli, 1981; Budavari, 1989). Nicotine is extracted by treatment with alkali and steam distillation or by extraction with solvents.

Artificial Sources: In addition to the natural release of nicotine by decomposition of tobacco plants, the compound may be introduced into the environment by the use of nicotine based insecticide preparations. According to the Swedish Chemical Inspectorate, the quantity of nicotine as an insecticide has dropped vigorously. However, the use of nicotine in different consumption products (cigarettes etc) cause an extensive distribution of the compound. The nicotine content in cigarettes is usually in the range of 8 - 15 mg/cigarette, and the compound is e.g. released to the air in the particulate phase of tobacco smoke (Tso, 1969). In humans no more than 25 % of the total nicotine content of a cigarette is absorbed by smokers who inhale (Reinhardt and Britelli, 1981).

Terrestrial Fate: When released to soil, nicotine is known to biodegrade to a variety of different products including oxynicotine, 3-pyridylmethyl ketone, 2,3-dipyridyl, N-methylmyosmine and purple crystalline pigment. In moist soil, chemical hydrolysis and volatilization are not expected to be important fate processes. Under alkaline condition, nicotine should be highly mobile (Hartley and Kidd, 1985).

Aquatic fate: Nicotine is expected to degrade if released into water. Nicotine in water is not expected to undergo chemical hydrolysis, bioaccumulate significantly in aquatic organisms, or volatilize (Hartley and Kidd, 1985).

Atmospheric fate: Nicotine is expected to degrade rather quickly in the presence of light and oxygen. A resinous product may form. In the ambient atmosphere, nicotine may react with photochemically generated hydroxyl radicals (vapor phase half-life approximately 24 h), or may be removed by wet deposition. Slight potential exists for direct photolysis since nicotine absorbs UV light only weakly above 290 nm (Hartley and Kidd, 1985).

Biodegradation: In mammalian systems (dogs, swine) nicotine is rapidly eliminated from the plasma with a half-life of some hours (1 - 2 h). Nicotine is mainly metabolized by the liver but may also be metabolized, to less extent, by the kidneys and lungs. The principal metabolites are cotinine and nicotine-1'-N-oxide. Both nicotine and its metabolites are excreted through the kidneys. Approximately 10-20 % of the unchanged nicotine is excreted in the urine.

In humans, nicotine is readily absorbed from the respiratory tract, buccal mucous membranes, nasal mucosa, and skin. Elimination of nicotine is biphasic with an half-life of about 2 hours. Nicotine is oxidized and hydroxylated by microsomal oxidases. The metabolites are considered less toxic than nicotine. Both nicotine and its metabolites are eliminated in the urine.

Abiotic degradation: In the atmosphere, nicotine may react with hydroxyl radicals (vapor phase half-life approximately 24 h), or may be removed by wet deposition. Nicotine is not expected to undergo chemical hydrolysis in water.

Bioconcentration: A bioconcentration factor of 5 was etimated for nicotine using a linear regression equation based on a measured log octanol/water partition coefficient of 1.17, suggesting that nicotine will not bioaccumulate significantly (Lyman et al, 1981; Martin and Worthing, 1977).

Soil Adsorption/Mobility: No experimental soil or sediment partition coefficients were available, however, under alkaline condition, nicotine should be highly mobile (Hartley and Kidd, 1985).

Volatilization from Water/Soil: Volatilization from water is not expected to be an important fate process.

Water Concentrations: Nicotine has been found in drinking water in several U. S. cities, e.g. finished water from Miami contained 3 mcg/l of nicotine (U. S. EPA). The compound has also been detected in fresh water fish in Great Lakes (Passino and Smith, 1987).

Effluent Concentrations: No data available.

Atmospheric Concentrations: The average nicotine exposure levels in public places ranges from 0.031 to 0.043 mg/m^3. The Threshold Limit Value (TLV) for nicotine is 0.5 mg/m^3 (ACGIH, 1990).

Nicotine concentrations in the exhaust vent, during manufacture of the Nicotine Inhaler, ranged 0.002 - 0.056 mg/m^3 (Kabi Pharmacia, 1991).

Probable Routes of Human Exposure: By inhalation or absorption through the nasal mucosa. Skin absorption or oral intake of nicotine based insecticides.

5.2 Other (inactive) ingredients

5.2.1. ETHANOL

SUBSTANCE IDENTIFICATION, CHEMICAL AND PHYSICAL PROPERTIES

Structure: CH_3CH_2OH

CAS Registry Number:	64-17-5
Molecular Formula:	C_2H_6O
Boiling Point:	78.5 °C
Melting Point:	-114.1 °C
Molecular Weight:	46.07
Log Octanol/Water Partition Coefficient:	-0.31
Water Solubility:	Infinite
Vapor Pressure:	59.03 mm Hg at 25 °C
Flash point:	12 °C

TOXICITY DATA

LD_{50}:	14 000 mg/kg, oral rat
LC_{50} Fish:	creek shub (*Semotilus astromaculatus*) >7 000 mg/l (24 h), fingerling trout 11 200 mg/l (24 h) (Verschueren, 1983)
EC_{50} Algae:	5000 mg/l (*Scenedesmus quadricauda*) (Verschueren, 1983)

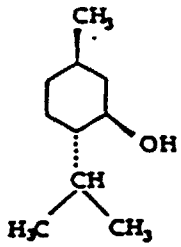
SUMMARY OF ENVIRONMENTAL FATE AND EXPOSURE POTENTIAL

Ethanol will enter the environment as emissions from its manufacture, use as a solvent and chemical intermediate, and release in fermentation and alcoholic beverage preparation. It naturally occurs as a plant volatile, microbial degradation product of animal wastes, and in natural fermentation of carbohydrates.
When spilled on land it is apt to volatilize, biodegrade, and leach into ground water, but no data on the rates of these processes can be found.

When released into water it will volatilize and probably biodegrade. It would not be expected to adsorb to sediment or bioconcentrate in fish. Although no data on its biodegradation in natural waters could be found, laboratory tests suggest that it may readily biodegrade and its detection in water systems may be due in part to its extensive use in industry with possible relatively steady and large levels of discharges.
When released into the atmosphere it will photodegrade in hours (polluted urban areas) to an estimated range of 4 to 6 days in less polluted areas. Rainout should be significant.
Human exposure will be primarily in occupational atmospheres and consumption products containing ethanol. Exposure will also occur from other contaminated atmospheres especially in proximity to industries and cities and ingestion of contaminated drinking water, as well as proximity to sources of natural release (Howard, 1990).

5.2.2. LEVOMENTHOL

SUBSTANCE IDENTIFICATION, CHEMICAL AND PHYSICAL PROPERTIES

Chemical name:	levomenthol, 2-isopropyl-5-methylcyclohexanol
CAS Registry Number:	89-78-1
Molecular Formula:	$C_{10}H_{20}O$
Boiling Point:	216 °C
Melting Point:	42/44 °C
Structure:	
Molecular Weight:	156,3
Water Solubility:	0.4 g/l
Log Octanol/Water Partition Coefficient:	3.25
Vapor Pressure:	1 mm Hg at 56 °C

TOXICITY DATA

LD_{50}: 3180 mg/kg, oral rat

Other effects: Levomenthol is an irritant

SUMMARY OF ENVIRONMENTAL FATE AND EXPOSURE POTENTIAL

Data on environmental fate of levomenthol is very sparse. When used as sole carbon source in a biodegradation study, 95.1 % of the COD was removed. The log octanol/water partition coefficient indicates a potential for bioaccumulation.

5.2.3. POROUS PLUG

SUBSTANCE IDENTIFICATION

CAS Registry number: 9002-88-4

Composition: HD Polyethylene

Molecular formula: $-[CH_2-CH_2-]_n-$

5.3 Materials for assembling of the Nicotine Inhaler

Materials for assembling of the Nicotine Inhaler are a cartridge ([redacted]), a mouth piece of polypropylene, and foils for the seals ([redacted]).

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The introduction of substances into the environment has been subdivided into three areas:

A. Introduction of substances into the environment by the manufacture, storage and internal transportation of the product
B. Introduction of substances into the environment by the use of the product
C. Introduction of substances into the environment by disposal of the product

A. Introduction of substances into the environment by the manufacture, storage and internal transportation of the product

1. Air Emissions
Air emissions during the manufacturing process of the Nicotine Inhaler include nicotine, ethanol, nitrogen and levomenthol.

Emissions of nicotine to the atmosphere during the manufacture of a batch of inhalers (750,000 units) is expected to be less than 25 mg. Ethanol emissions from the full scale production of the units are expected to be low (<1,000 kg/year). The air emission of levomenthol is expected to be about 10 times lower than the air emission of nicotine.

2. Water Pollution

Discharge to effluent wastewater streams during manufacturing and cleaning procedures include ethanol and a small amount of nicotine (see 'liquid non-hazardous waste', p. 12).

3. Spill Control Procedures

The procedure for the application of liquid nicotine has been designed as a closed system. In addition to the closed system, spill prevention procedures are provided by safe handling and transportation procedures. These procedures are outlined below:

- All employees are instructed to transport nicotine in closed containers that have been placed in leak proof, vapor tight secondary containment. The secondary container is constructed of either plastic or metal.

- Nicotine is dispensed into another container under a local exhaust system. A secondary container is placed under the primary container to eliminate potential spills during dispensing procedure.

- Employees working with nicotine follow written procedures for the use of personal protective equipment (e.g. air-supplied respirator, protective suit and gloves, and face shield); these procedures are operation specific.

All employees working with nicotine are trained in the procedures for handling a spill.

4. Hazardous and Non-Hazardous Waste Emissions

There are four categories of waste generated during the manufacturing and cleaning processes: solid hazardous waste, solid non-hazardous waste, liquid hazardous waste and liquid non-hazardous waste.
All handling of hazardous waste is in accordance with applicable regulatory requirements. Shipments are properly manifested and reported as required by the regulating agencies.

a) Solid Hazardous Waste

All solid materials, including clothing and gloves, that are potentially contaminated with nicotine are classified as "Hazardous waste/pharmaceutical waste" according to AFS 1989:2 (Swedish Work Environment Act). The nicotine contaminated waste is transported in a sealed container and incinerated at an approved facility (Sydvästra Skånes Avfallsaktiebolag, SYSAV, Malmö, Sweden).
Nicotine is decomposed to carbon dioxide, water, carbon monoxide and nitrogen oxides when incinerated. The ash residue from the incineration is landfilled.

b) Solid Non-Hazardous Waste
Non-hazardous waste is landfilled at Nordvästra Skånes Renhållnings AB (NSR), Helsingborg, Sweden.

c) Liquid Hazardous Waste
All liquid hazardous waste is incinerated by Svensk Avfallskonvertering AB (SAKAB) at a permitted hazardous material treatment facility located in Kumla, Sweden.
Classification and transportation of hazardous waste is in accordance with the Swedish "Hazardous Waste Act" and the regulations concerning transportation of hazardous waste.

d) Liquid Non-Hazardous Waste
Process wastewater contaning ethanol and 0.1 - 0.2% nicotine is first collected in a tank and then slowly released into the wastewater system. The ethanolic wastewater is treated at the municipal sewage plant where it serves as a carbon source for the nitrogen reduction treatment step. The above procedure has been agreed by the local environmental authority and the sewage plant (permitted by the City of Helsingborg, April 10, 1995).
Biochemical oxygen demand (BOD), chemical oxygen demand (COD), suspended matter and pH are monitored in effluent water.

B. Introduction of substances into the environment by the use of the product

Introduction of nicotine and its metabolites into the environment is expected to occur via excretion by patients using this product. However, the use of this product is not expected to result in any increase in the amount of nicotine and its metabolites entering the environment.
The nicotine in this product is chemically identical to the nicotine which occurs naturally in tobacco. The inhaler delivers, on average, the amount of nicotine equivalent to smoke inhaled from approximately 3 - 5 cigarettes.
Once absorbed into the body, nicotine is metabolized, distributed and excreted in the same manner regardless of the source. Since the product is intended as a nicotine replacement therapy for smokers attempting to stop smoking, the introduction of nicotine and its metabolites would not be affected by the use of this product.

In humans, nicotine is readily absorbed from the respiratory tract, buccal mucous membranes, nasal mucosa, and skin. Elimination of nicotine is biphasic in man with a terminal half-life of about 2 hours. Nicotine is oxidized and hydroxylated by microsomal oxidases, which yield less toxic metabolic products. Cotinine formation is apparently through the immediate hydroxylation product 2-hydroxynicotine.

C. Introduction of substances into the environment by disposal of the product

The used systems and their packaging components will be disposed of by the patient. The inhaler and packaging material will be disposed as household

solid waste by the patient. The residual nicotine content in the inhaler after use, is approximately 6 mg. This is less than the amount of nicotine in one cigarette and is equivalent to the amount found in approximately 1 - 2 cigarette butts.
After usage of the inhaler, the cartridge should be separated from the mouthpiece and disposed of in a safe way out of the reach of children or pets.

D. Compliance with emission standards

Pharmacia (Helsingborg plant) is in compliance with applicable national, regional and local environmental and occupational health statutes and emission standards.
Pharmaceutical production at the Helsingborg plant is permitted according to the Swedish Environment Protection Act by Licence 1992-07-08, 2410-15903/91 covering pharmaceutical production, air emissions, waste product handling, returns/rejects treatment, noise reduction and control program.
All wastewater streams are discharged to the municipal sewage system. Effluent wastewater monitoring (four days a month) includes BOD, COD, suspended matter, and pH.
As pointed out earlier in this report (see 'liquid non-hazardous waste', p. 12), waste ethanol from the manufacture of the Nicotine Inhaler, containing a small amount of nicotine, is discharged into wastewater for biodegradation at the municipal wastewater treatment plant. The company has a special licence that permits the discharge of ethanol into wastewater (issued by the City of Helsingborg, April 10, 1995).
The annual environmental report includes detailed information about emissions into the atmosphere and wastewater, use of natural resources and raw materials, and amount and processing of waste.

Manufacture of the Nicotine Inhaler is not expected to affect compliance with current emission limits. Emissions caused by the estimated fifth year production volume will also be within the licence limits.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Nicotine
Air monitoring for nicotine emissions has been performed at the point of exhaust for the machine used for manufacturing of Nicotine Inhaler.
The results indicate that loss of nicotine to the atmosphere during the manufacture of a pilot scale batch (150,000 units) of inhalers is expected to be less than 25 mg. The highest concentration of nicotine in the vent was 0.056 mg/m^3, which may be compared to the average nicotine exposure levels in public places which may range from 0.031 to 0.043 mg/m^3.
Nicotine is expected to degrade if released into air, water, and soil. Nicotine is not expected to bioaccumulate significantly.
Detailed information about the environmental fate of nicotine is presented in Item 5.

Ethanol
Ethanol emissions from the full scale production of the units are expected to be low (<1,000 kg/year).
When released into the atmosphere it will photodegrade. Rainout should be significant. When released into water it will volatilize and probably biodegrade. It would not be expected to adsorb to sediment or bioconcentrate in fish. When spilled on land it is apt to volatilize, biodegrade, and leach into ground water, but no data on the rates of these processes can be found.

Additional information about the environmental fate of ethanol is presented in Item 5.

Levomenthol
During production of the units, the air emission of levomenthol is expected to be about 10 times lower than the emission of nicotine.

Other emissions
The system and packaging material will be disposed of as household solid waste by the patient. The amount of residual nicotine remaining in one inhaler after use is approximately 6 mg. This is less than the amount of nicotine in one cigarette and corresponds to the residual amount of nicotine found in 1 - 2 cigarette butts (2 cm). This amount is approximately equivalent to the typical amount of nicotine waste generated by a smoker and is not perceived to cause any harmful effects to the environment.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Nicotine
The Nicotine Inhaler is not expected to alter significantly the concentration of nicotine, its metabolites, degradation products or its constituent parts in the environment.

Environmental fate and exposure data for nicotine are presented in Item 5. From these data and from the estimation of levels in the environment due to the production and use of the Nicotine Inhaler, it can be concluded that the small amount of nicotine emitted to the environment is well below levels associated with adverse effects in laboratory animals and organisms in the environment.

Ethanol, nitrogen and levomenthol
The ethanol, nitrogen and levomenthol emissions are small and are not expected to have any environmental impact.

9. USE OF RESOURCES AND ENERGY

The pilot scale manufacturing facility for Nicotine Inhaler occupies about 900 m^2 at the Pharmacia plant in Helsingborg, Sweden. Utilities are pur-

chased from Sydkraft Electric Company, Helsingborg Energi AB (natural gas) and Helsingborg Municipal Water system.
Electrical energy is mainly used for the process (for a full-scale production of 250 x 10^6 units/year the energy consumption is estimated to about 80,000 kWh/year). Water is mainly used for the cleaning procedures. The use of renewable and non-renewable natural resources is considered insignificant.

Waste material generated through the manufacturing process are mainly incinerated as described in 6.A.4. Waste products generated by use of the product are minimal and will be disposed of as household waste.

The product will be transported via common carrier within the United States and overseas. Due to the very small size of the product container, the energy required to transport the product is not expected to significantly affect the availability of resources.

10. MITIGATION MEASURES

Mitigation measures for limiting employee exposure to, or outside environmental release or leakage of, potentially harmful substances have been taken.
In addition to the use of closed systems for the different manufacturing steps, spill prevention procedures for nicotine liquid is provided by safe handling and transportation procedures.
Material Safety Data Sheets for nicotine, ethanol, and levomenthol are available for all employees who work in all phases of the production of the Nicotine Inhaler. All employees are trained in the safe handling of nicotine and nicotine products.
Nicotine contaminated waste products generated in the manufacture of the Nicotine Inhaler are incinerated at permitted hazardous incineration facilities.

The technical fire protection is equipped with extension fire detectors in all areas which, in case of fire, automatically will alert the municipal rescue services. In all areas fire houses and fire extinguishers are installed. Fire doors and safety locks are installed in the manufacturing facilities.

11. ALTERNATIVES TO PROPOSED ACTION

No alternatives have been considered due to the negligible impact on the environment. Furthermore, an alternative of no action would deprive smokers of a valuable therapy for smoking cessation and could increase the environmental pollution associated with the smoking of cigarettes.

12. LIST OF PREPARERS

Bengt Bosson Head of Development Department, Pharmacia Consumer Pharma

Education: M. Eng, Chemistry; D. Eng., Inorganic Chemistry, Lund University, Sweden
Experience: 5 years experience in the chemical industry, 15 years experience in the pharmaceutical industry

Torbjörn Brorson Environmental Manager, Pharmacia Corporate Environment & Risk Management

Education: B. Sc., Chemistry and Biology; M. Sc., Occupational Hygiene; Dr. Med. Sc., Occupational and Environmental Medicine, Lund University, Sweden
Experience: 15 years experience in occupational and environmental issues, 6 years in the pharmaceutical industry

Göte Friberg Development staff, Pharmacia Consumer Pharma

Education: Mechanical Engineer, graduated from the Technical College of Jönköping
Experience: Different mechanical industries 1961 - 1967. At the packaging department at LEO since 1967. Manager for different production and packaging departments 1968 - 1988. Engaged in technical development and support 1989 - 1990. Technical manager, Business unit Nicorette since 1991.

Folke Morén Senior Consultant, Morenco Pharmaceuticals AB

Education: M. Sc. Pharm; Ph. D. in Galenical Pharmacy; Associate Professor in Galenical Pharmacy, University of Uppsala, Sweden
Experience: Associate Director, Pharmaceutical Research, AB Draco, Lund, Sweden 1966 - 1973. Director, Pharmaceutical Research, AB Draco, Lund, Sweden 1974 - 1980. Senior Director, Pharmaceutical Research, AB Draco, Lund, Sweden 1981 - 1985. Director, Hospital Pharmacy, Apoteksbolaget AB, Helsingborg, Sweden 1986 - 1990. Senior Consultant, Novecon Research AB, Lund, Sweden 1989 - present. Managing Director, Morenco Pharmaceutical AB; Malmö, Sweden, 1988 - present.

Lena Persson Head of Chemicals Safety Department, Pharmacia Consumer Pharma

Education: Pharmacist, graduated from the Royal Pharmaceutical Institute, Stockholm, Sweden

Experience: Employed at LEO 1961. Engaged in pharmaceutical development 1961 - 1964. Production Supervisor 1969 - 1978. Since 1978 engaged within Technical Administration Development. Responsible for labour protection, GMP, inspection and education, since 1987 Head of the Chemicals Safety Department at Pharmacia Consumer Pharma, Helsingborg

Hans Thulin Industrial Hygienist, Pharmacia Consumer Pharma

Education: B. Sc., Chemistry and Environmental items; Lic. Eng., Working Environment, Lund University and Lund Institute of Technology, Sweden

Experience: 19 years as an Industrial Hygienist, 9 years in the pharmaceutical industry

13. CERTIFICATION

The undersigned official certifies that the information presented in the Environmental Assessment is true, accurate, and complete to the best knowledge of the firm.

Torbjörn Brorson, Dr.
Environmental Manager
Corporate Environment & Risk Management
Pharmacia AB

15/8 1995
date

14. REFERENCES

ACGIH (1990). Threshold limit values.

Budavari, S. (1989). The Merck Index. 11th ed., p 1030, Rahway, New Jersey.

Hartley, D. and Kidd, H. (1985). The Agrochemical Handbook. The Royal Society of Chemistry, United Kingdom.

Howard, P. H. (1990). Handbook of Environmental Fate and Exposure Data for Organic Chemicals. Lewis Publishers, Michigan.

Kabi Pharmacia (1991). Measurement of nicotine concentrations in the exhaust vent during manufacture of Nicotine Inhaler. Kabi Pharmacia.

Lyman, W. J. (1981). Handbook of Property Estimation Methods, McGraw-Hill, New York.

Martin, H. and Worthing, C. R. (1977). The Pesticide Manual, 5th ed., British Corp. Protection Council, England.

Passino D. R. M. and Smith S. B. (1987). Acute bioassays and hazard evaluation of representative contaminants detected in Great Lakes fish. Environ. Toxicol. Chem. 6:901-907.

Perry C. M. and Smith S. B. (1988). Toxicity of six heterocyclic nitrogen compounds to *Daphnia pulex*. Bull. Environ. Contam. Toxicol. 41:604-608.

Reinhardt C. F. and Brittelli M. R. (1981). Heterocyclic and miscallaneous nitrogen compounds. In: Patty's Industrial Hygiene and Toxicology pp 2740-2745.

Tso, T. S. (1969). Kirk-Othmer Encycl. of Chemical Technology 2nd ed., Wiley 20, 515-517 New York.

U. S. EPA. Preliminary Assessment of Suspected Carcinogens in Drinking Water, Washington, D. C.

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals. Van Nostrand Reinhold, New York.

Weiss, G. (1986). Hazardous Chemicals Data Book, 2nd ed Noyes Data corp, Park Ridge, NJ.

HELSINGBORG

APPENDIX I

Certification of Compliance

Pharmacia AB, Consumer Pharma, is in compliance with applicable national, regional and local environmental and occupational health statues and emission standards.

Pharmaceutical production at the Helsingborg plant is permitted according to the Swedish Environmental Protection Act by Licence 1992-07-08, 2410-15903/91, covering pharmaceutical production, air emissions, waste product handling, returns/rejects treatment, noise reduction and control program.

Emissions are reported in a mandatory annual environmental report submitted to the Environmental Authority of the City of Helsingborg. The environmental report for 1994 shows compliance with all applicable licence conditions.

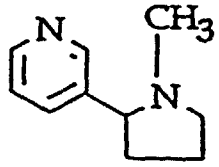
Gregor Holmgren
Director of the local Environmental Authority
in Helsingborg

MILJÖKONTORET
251 89 HELSINGBORG - BESÖKSADRESS : JÄRNVÄGSGATAN 22 - TELEFON 042-10 30 00 /vx/ - FAX 042-10 30 44 - POSTGIRO : 47 44 01-9

Pharmacia

SAFETY DATA SHEET

NICOTINE



CAS NUMBER 54-11-5
DATE PREPARED April 1994, Rev. 0

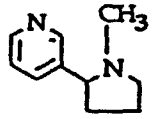
The EEC version
Chemical control department, Helsingborg, Sweden/Lena Persson

Postal address	Visiting address	Telephone	Telefax
Kabi Pharmacia AB Box 941 S-251 09 Helsingborg Sweden	Norrbroplatsen 2 Helsingborg	Nat 042 10 40 00 Int +46 42 10 40 00	Nat 042 13 68 50 Int +46 42 13 68 50

SAFETY DATA SHEET

1. Identification of the substance and of the company.

COMMON NAME	Nicotine
SYNONYMS	Nicotinum
EINECS No.	2001933
COUNCIL DIRECTIVE 67/548/EEC ANNEX 1 No.	614-001-00-4
CAS NUMBER	54-11-5
CHEMICAL NAME	Pyridine, 3-(1-methyl-2-pyrrolidinyl)-
FORMULA	$C_{10}H_{14}N_2$



MOLECULAR WEIGHT	162,23
COMPANY NAME	Pharmacia AB
COMPANY ADDRESS AND TELEPHONE NUMBER	Box 941 S-25109 Helsingborg Sweden Telephone Int + 46 42 104000 Telefax Int + 46 42 136850
DATE AND REVISION	April 1994, rev. 0
EMERGENCY TELEPHONE NUMBER	

Pharmacia AB	SAFETY DATA SHEET
COMMON NAME	Nicotine
CAS NUMBER	54-11-5
DATE PREPARED	April 1994 rev. 0

2. Information on substance.

PRINCIPAL HAZARDOUS COMPONENT(S)	Nicotine Pure material
APPEARANCE AND ODOUR	Colourless to pale yellow oily liquid, with a slight fishy odour when warm. Turns brown on exposure to air.
EXPOSURE LIMIT VALUES	ACGIH TLV (1992 - 1993): 0,5 mg/m^3 (TWA) Skin

3. Hazards identification

HEALTH HAZARDS

TOXIC IF SWALLOWED. VERY TOXIC IN CONTACT WITH SKIN.

GENERAL INFORMATION

Nicotine is the best known of the alkaloids in tobacco. It is used in medicine as an aid to smoking cessation and as an insecticide.

ROUTES OF EXPOSURE

Nicotine can affect the body if it is inhaled, if it comes in contact with the eyes or skin, or if it is swallowed. It may rapidly enter the body through the skin.

SYMPTOMS AND SIGNS

Short-term exposure.
The action of nicotine is rapid either after breathing it, swallowing it, or absorbing it through the skin. Exposure may cause a burning sensation of the mouth and throat, abdominal pain, nausea, vomiting, and diarrhoea. It may also cause headache, sweating, dizziness, hearing and visual disturbances, confusion, weakness, and incoordination. The heart may beat irregularly or stop. Trembling and convulsions, faintness, shortness of breath, and collapse may occur which may be followed by death from respiratory paralyses.
Exposure of the eyes and skin may cause irritation.

FIRE AND EXPLOSION HAZARDS

Nicotine is combustible. Fire or excessive heat produce toxic gases and vapours, which, mixed with air, may be explosive (nitrogen oxides, carbon dioxide and carbon monoxide).

ENVIRONMENTAL HAZARDS	If released to soil or water, nicotine is expected to biodegrade. Nicotine is expected to degrade rather quickly in the atmosphere in the presence of light and oxygen. Nicotine will not bioaccumulate in living organisms.

4. First-aid measures

Inhalation:	Move victim to fresh air. If breathing is difficult, give oxygen and if breathing has stopped, perform artificial respiration. Keep the affected person warm and at rest. Get medical attention as soon as possible.
Skin:	Remove immediately contaminated clothing and flush the contaminated skin with large amounts of water. Get medical attention immediately.
Eyes:	Immediately rinse with large amounts of water (separate the eyelids with fingers). Get medical attention immediately.
Ingestion:	Immediately give some glasses of milk or water and if possible 15 - 50 g of activated charcoal (charcoal suspension). Try to get the person to vomit by having him touch the back of his throat with his finger. Do not make an unconscious person vomit. Get medical attention immediately.

5. Fire-fighting measures

EXTINGUISHER MEDIA	Alcohol foam, dry chemical, carbon dioxide as appropriate for surrounding fire and materials. Water may cause frothing if it gets below surface of liquid and turns to steam. However, water fog gently applied to surface will cause frothing which will extinguish the fire.
SPECIAL FIRE FIGHTING PROCEDURES	Evacuate personnel to safe area. Nicotine is dangerous to the health of the firefighters. A few whiffs of the vapour could cause death, vapour or liquid could be fatal on penetrating their normal full protective clothing.
FIRE AND EXPLOSION HAZARDS	Emits nitrogen oxides, carbon dioxide and carbon oxide under fire conditions. There is a moderate explosion hazard when exposed to heat or flame.

6. Accidental release measures.

STEPS TO BE TAKEN IN CASE MATERIAL IS SPILLED OR RELEASED	Nicotine should be absorbed in absorbent material (eg vermiculite). Sweep up spillage carefully, be aware of the health hazards!

Small spill could be swabbed up with a paper towel or a disposable mop and water.

Place spillage, including the absorbent material, in appropriate container for waste disposal.

CLEANING METHODS

Wash premises, equipment and working surfaces with acidified water (pH =3).
Clothing which has had any possibility of being contaminated with nicotine should be placed in closed containers for the removal of nicotine from the clothing. If the clothing is to be laundered or otherwise cleaned to remove the nicotine, the person performing the operation should be informed of nicotine's hazardous properties.

WASTE DISPOSAL METHODS

Dispose of nicotine waste by incineration in accordance with national and local regulations.

7. Handling and storage

HANDLING

Do not handle or use nicotine until safety preautions in the Safety Data Sheet have been read and understood.

Good care should be taken in handling nicotine.
Ship in packages constructed to minimize risk of breakage.
Do not store food and do not eat, smoke, drink or chew gum near of preparation or storage; do not apply makeup or use cosmetics in an area contaminated with nicotine.
If possible, work in closed systems. Otherwise, use ventilated cupboard or specially designed local exhaust ventilation.
Washing facilities including shower should be available within the working area.
Eye-wash fountain should be available.
Working place and methods must be designed to avoid direct contact with nicotine.

STORAGE

Store in room temperature in a tightly closed container.

8. Exposure controls/personal protection

PERSONAL MEANS OF PROTECTION

Wear suitable respiratory equipment. Fullface mask with gasfilter A and dustfilter P 3 or compressed-air mask or hood. Wear suitable gloves and when necessary protective clothing giving total body cover.

9. Physical and chemical properties

Appearance:	Colourless to pale yellow oily liquid. Turns brown on exposure to air.
Odour:	A slight fishy odour when warm.
Boiling point:	+ 246 - 247°C
Melting point:	- 79°C
Flash point:	+ 102°C
Autoignition temperature:	+ 240°C
Explosive properties:	Explosive limits in air, % by volyme Lower: 0,7; Upper: 4
Vapour pressure:	0,0057 kPa
Vapour density (air=1)	5,6
Density:	1,01 g/cm^3
Solubility: - water	Miscible below 64 ° C
- organic solvents	Soluble in ethanol, ether and chloroform
Log partition coefficient octanol-water (logK_{ow}):	1.17 at pH 7.

1 ppm = 6,64 mg/m^3
1 mg/m^3 = 0,15 ppm

10. Stability and reactivity

STABILITY	Material is stable at room temperature, if protected from oxygen, e g by nitrogen.
CONDITIONS TO AVOID	Heat or flames.
MATERIALS TO AVOID	Oxidizing materials.
SPECIAL PRECAUTIONS	Nicotine will attack some forms of plastics, rubber, and coatings.

11. Toxicological information

GENERAL INFORMATION

Nicotine in solution causes a transient stimulation, followed by depression or paralyses of the central nervous system, peripheral autonomic ganglia, and nerve endings in skeletal muscle; it also direct stimulates smooth muscle.
Many fatal human cases of nicotine intoxication have occurred, usually as a result of accidental or suicidal ingestion of nicotine insecticides. Nicotine is readily absorbed through the skin; in fatal cases of intoxication death nearly always occur within 1 hour and has occurred within 1 minute; the fatal adult dose is about 60 mg. Recovery usually occurs if the victim survives 1 to 4 hours.

LD_{50} oral rat:	50 mg/kg
Mutagenicity:	Negative in Ames test

Reproductive toxicity:

Maternal smoking during pregnancy is associated with increased risk of spontaneous abortion, low birth weight and stillbirth.

12. Ecological information

Natural sources: Nicotine is an alkaloid contained in the tobacco plants *Nicotiana tabacum* and *Nicotiana rustica*. A tobacco leaf usually has a concentration of 1 - 2 % nicotine.

Artificial sources: Nicotine may be introduced into the environment by the use of nicotine based insecticide preparations or by the use of consumption products such as cigarettes etc.

Terrestrial fate: When released to soil, nicotine is expected to biodegrade to a variety of different products including oxynicotine, 3-pyridylmethyl ketone, 2, 3- dipyridyl, N-methymyosmine and purple crystalline pigment.
In moist soil, chemical hydrolyses and volatilation are not expected to be important fate processes.
Under alkaline condition, nicotine should be highly mobile.

Aquatic fate: If released into water nicotine is expected to degrade and it would not be expected to undergo chemical hydrolyses, bioaccumulate significantly in aquatic organisms, or volatilize.

Atmospheric fate: Nicotine is expected to degrade rather quickly in the presence of light and oxygen.

Biodegradation: In mammalian systems (dogs, swine, humans) nicotine is rapidly eliminated from the plasma with a half-life of some hours.
Both nicotine and its metabolites are eliminated in the urine.
The metabolites are considered less toxic than nicotine.

Abiotic degradation: In the atmosphere, nicotine may react with hydroxyl radicals (vapor phase half - life of about 24 h), or may be removed by wet deposition.
Nicotine is not expected to undergo chemical hydrolyses in water.

Bioconcentration: Nicotine will not bioaccumulate significantly.

13. Disposal considerations

Nicotine waste should be incinerated in accordance with national and local regulations.

14. Transport information

ADR	Class: 6.1 Number/letter: 77(b) Name: Nicotine / Nicotine. Label: 6.1 Tramcard: Yes
DGR	Class: 6.1 Pkt. group: II Name: Nicotine Label:Poison
IMDG	Class: 6.1 Page: 6203 Pkg group: II Name: NICOTINE EmS No.: 6.1-02 MFAG: 800 Label: 6 Poison
UN:nr	1654

15. Regulatory information

COUNCIL DIRECTIVE of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. (67/548/EEC)	Symbol: Skull and crossbones. Main text:TOXIC IF SWALLOWED. VERY TOXIC IN CONTACT WITH SKIN.
	Classification: Very toxic
	R : 25 - 27 Toxic if swallowed. Very toxic in contact with skin.
	S : 36/37 - 45 Wear suitable protective clothing and gloves. In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

16. Other information

Disclaimer: The information is given in good faith being based on the latest knowledge available to Pharmacia AB . Pharmacia AB disclaims any express or implied warranty as to the accuracy of the above information and shall not be held liable for any incidental or consequential damages resulting from reliance on the above information.

FONSI FOR NDA 20-714

cc:

NDA 20-714/Original/Hand JRoss
HFD-170/Div. File
HFD-170/JMRoss
FONSI FILE NDA 20-714
Docket File 20714/HFD-537
FOI Copy HFD-205
Document ID: EA20714.3/5/97