CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20658

CHEMISTRY REVIEW(S)

Division of Neuropharmacological Drug Products **NDA: 20-658** OCT 28 1996

Review of Chemistry, Manufacturing, and Controls

		Letter Date	Stamp Date	Rec'd by Chemist	Completed
Initial Submission		02-Jan-96	02-Jan-96	08-Jan-96	15-Mar-96
Chemistry Review	#1		**Sponsor**	SmithKline Beecham Pharmaceuticals	
Review Chemist	D. Scarpetti, Ph.D.		**Address**	PO Box 7929 One Franklin Plaza Philadelphia, PA 19101	

Product Name

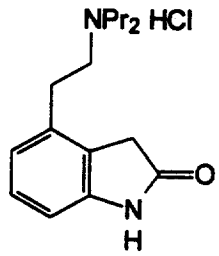
Proprietary: Ropinirole
Nonproprietary/USAN: Ropinirole Hydrochloride, Ropinirole Tablets
Code Name/#: SK&F 101468 (free base), SK&F-A (HCl salt)

Chemical Name, Structural and Molecular Formula

4-[2-(Dipropylamino)ethyl]-2-indolinone monohydrochloride, $C_{16}H_{24}N_2O \cdot HCl$ (MW 296.84)

Dosage Form/Route of Administration

Oral film coated tablet 0.25, 0.50, 1, 2 and 5 mg tablet/Oral



Pharmacological Category/Indication

D2 receptor agonist/Symptomatic Treatment of Parkinson's Disease

Supporting Documents

IND

Remarks

The drug substance is synthesized by

Conclusions and Recommendations

Upon validation of the analytical methods the recommendation is for approval of NDA 20-658, Ropinirole.

cc:
Original NDA 20-658
HFD-120/Division File
HFD-120/DScarpetti
HFD-120/RNighswander
HFD-120/SWBlum
Init by: SWB/

SWB 10/28/96

David Scarpetti 8/8/96

David Scarpetti, Ph.D., Chem Reviewer

Division of Neuropharmacological Drug Products

NDA: 20-658

Review of Chemistry, Manufacturing, and Controls

	Letter Date	Stamp Date	Rec'd by Chemist	Completed
Initial Submission	02-Jan-96	02-Jan-96	08-Jan-96	15-Mar-96

Chemistry Review #1A **Sponsor** SmithKline Beecham Pharmaceuticals

Review Chemist D. Scarpetti, Ph.D. **Address** PO Box 7929
One Franklin Plaza
Philadelphia, PA 19101

Product Name

Proprietary: Ropinirole
Nonproprietary/USAN: Ropinirole Hydrochloride, Ropinirole Tablets
Code Name/#: SK&F 101468 (free base), SK&F-A (HCl salt)

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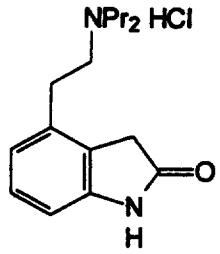

Pharmacological Category/Indication

D2 receptor agonist/Symptomatic Treatment of Parkinson's Disease

Supporting Documents

IND 31,712

Remarks

This addendum to CMC Review #1 notes the sponsor did not describe acceptance testing for the plastic packaging components for the drug product.

Conclusions and Recommendations

A comment requesting the sponsor provide acceptance testing for the plastic packaging components has been added to the action letter.

cc:
Original NDA 20-658
HFD-120/Division File
HFD-120/DScarpetti
HFD-120/RNighswander
HFD-120/SWBlum
Init by: SWB/ 12/13/96

David Scarpetti, Ph.D., Chem Reviewer 12/13/96

Division of Neuropharmacological Drug Products **NDA: 20-658**
Review of Chemistry, Manufacturing, and Controls

MAY 30 1997

	Letter Date	Stamp Date	Rec'd by Chemist	Completed
Initial Submission	02-Jan-96	02-Jan-96	08-Jan-96	15-Mar-96
Amendment N(AZ)	28-Mar-97	31-Mar-97	01-Apr-97	20-May-97

Chemistry Review #2 **Sponsor** SmithKline Beecham Pharmaceuticals

Review Chemist D. Scarpetti, Ph.D. **Address** PO Box 7929
One Franklin Plaza
Philadelphia, PA 19101

Product Name
Proprietary: Ropinirole
Nonproprietary/USAN: Ropinirole Hydrochloride, Ropinirole Tablets
Code Name/#: SK&F 101468 (free base), SK&F-A (HCl salt)

Chemical Name, Structural and Molecular Formula
4-[2-(Dipropylamino)ethyl]-2-indolinone monohydrochloride, $C_{16}H_{24}N_2O \cdot HCl$ (MW 296.84)

Dosage Form/Route of Administration
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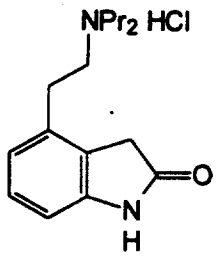


Pharmacological Category/Indication
D2 receptor agonist/Symptomatic Treatment of Parkinson's Disease

Supporting Documents

Remarks
This information amendment addresses deficiencies cited in the first CMC review.

Conclusions and Recommendations
Status: NDA 20-658 is approvable with respect to chemistry, manufacturing and controls.
Site Inspections:All sites acceptable with compliance as of 11-Apr-97.
Environmental Assessment. Reviewed and deficient as of 15-Oct-96.
Methods Validation. Packages sent to validating labs 10-Apr-97, no results yet (no problems anticipated).

cc:
Original NDA 20-658
HFD-120/Division File
HFD-120/DScarpetti
HFD-120/RN[redacted]
HFD-120/SWBlum
Init by: SWB/ 5/29/97

5/21/97
David Scarpetti, Ph.D., Chem Reviewer

Division of Neuropharmacological Drug Products **NDA: 20-658**
Review of Chemistry, Manufacturing, and Controls

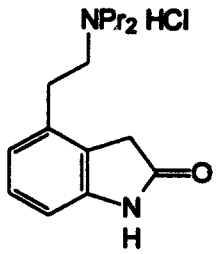
	Letter Date	Stamp Date	Rec'd by Chemist	Completed
Initial Submission	02-Jan-96	02-Jan-96	08-Jan-96	15-Mar-96
Amendment N(BC)	20-Jun-97	24-Jun-97	24-Jun-97	01-Jul-97

Chemistry Review #3 **Sponsor** SmithKline Beecham Pharmaceuticals

Review Chemist D. Scarpetti, Ph.D. **Address** PO Box 7929
One Franklin Plaza
Philadelphia, PA 19101

Product Name
Proprietary: Ropinirole
Nonproprietary/USAN: Ropinirole Hydrochloride, Ropinirole Tablets
Code Name/#: SK&F 101468 (free base), SK&F-A (HCl salt)

Chemical Name, Structural and Molecular Formula
4-[2-(Dipropylamino)ethyl]-2-indolinone monohydrochloride, $C_{16}H_{24}N_2O \cdot HCl$ (MW 296.84)



Dosage Form/Route of Administration
Oral film coated tablet 0.25, 0.50, 1, 2 and 5 mg tablet/Oral

Pharmacological Category/Indication
D2 receptor agonist/Symptomatic Treatment of Parkinson's Disease

Supporting Documents
CMC reviews 1, 1A & 2.

Remarks
The sponsor describes the detection of a

Conclusions and Recommendations
See CMC review #2 for updated status of CMC review components. The recommendation for 20-658 is for approval.

cc:
Original NDA 20-658
HFD-120/Division File
HFD-120/DScarpetti
HFD-120[redacted]
HFD-120/SWBlum
Init by: SWB/ SWB 7/15/97

7/15/97
David Scarpetti, Chem Reviewer

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20658

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-658

Requip™ (ropinirole hydrochloride) Tablets

Division of Neuropharmacological Drug Products

(HFD-120)

CENTER FOR DRUG EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

for

NDA 20-658

Requip™ (ropinirole hydrochloride) Tablets

REVIEW DIVISION: HFD-120

CENTER FOR DRUG EVALUATION AND RESEARCH

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

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 a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for REQUIP™, SmithKline Beecham has prepared an environmental assessment in accordance with 21 CFR 25.31a (a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Ropinirole hydrochloride is a chemically synthesized drug which is administered as tablets for the treatment of Parkinson's disease. The drug substance is manufactured by SmithKline Beecham (Manufacturing) Limited, Cork, Ireland with an alternative manufacturing site at SmithKline Beecham Pharmaceuticals, Worthing, West Sussex, UK. The drug product manufacture and packaging occurs at SmithKline Beecham, Crawley, UK. The finished drug product will be used in throughout the United States.

Ropinirole may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. The applicant provided ecotoxicological data showing that the most sensitive organism evaluated was Bluegill sunfish. At a 96 hour acute exposure, the EC_{50} was 11 mg/L and the NOEC was 3.7 mg/L which indicates no significant environmental effects should occur at the expected environmental concentration.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Rejected or returned drug product will be disposed of at a permitted high temperature incinerator at SmithKline Beecham, Bristol, TN or Ogden Martin Systems of Lake, Inc., Okahumpka, FL. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

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

6/3/97
DATE

Prepared by
Phillip G. Vincent, Ph.D
Environmental Scientist
Center for Drug Evaluation and Research

6/3/97
DATE

Concurred
Nancy Sager
Acting Supervisor/Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

ENVIRONMENTAL ASSESSMENT
Ropinirole (SK&F 101468) Tablets
NDA # 20-658

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Ropinirole (SK&F 101468) Tablets
NDA # 20-658

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NOTE: The following Confidential Attachments are not found in the Freedom of Information Act copy of this Environmental Assessment.

ENVIRONMENTAL ASSESSMENT
Ropinirole (SK&F 101468) Tablets
NDA # 20-658

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Ropinirole (SK&F 101468) Tablets
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ENVIRONMENTAL ASSESSMENT

Ropinirole (SK&F 101468) Tablets

NDA 20-658

1. **DATE:** 26 September 1995

2. **NAME OF APPLICANT:** SmithKline Beecham Pharmaceuticals

3. **ADDRESS:** Four Falls Corporate Center
Route 23 and Woodmont Avenue
P.O. Box 1510
King of Prussia, PA 19406

4. DESCRIPTION OF THE PROPOSED ACTION:

4.1. Description of the Requested Approval

SmithKline Beecham Pharmaceuticals is requesting approval to manufacture, package and market ropinirole (SK&F 101468) Tablets (NDA # 20-658) for the treatment of Parkinson's disease. SK&F 101468-A (ropinirole HCl) is a novel, potent, and selective dopamine-2 agonist.

4.2. Need for the Proposed Action

The therapeutic indication for ropinirole (SK&F 101468) Tablets is for the treatment of Parkinson's disease, which affects about 1 in 1000 of the adult population. Patients suffer from progressive impairment of motor function and many also show associated depression and cognitive impairment. Ropinirole was developed for the symptomatic treatment of Parkinson's disease, both as early therapy in patients not treated with L Dopa and as adjunct therapy with L Dopa. Ropinirole is well absorbed in man, and is extensively metabolized (see Item 7.1).

This Environmental Assessment reflects effluent discharges based on estimated production of drug substance and product during the 5th year of production, as well as detailed information on the waste treatment and disposal processes at SmithKline Beecham Pharmaceuticals facilities in Worthing, England (U.K.); SmithKline Beecham (Manufacturing) Limited in Cork (Ireland) for drug substance production, and Crawley, England (U.K.) for drug product production.

The manufacture of ropinirole drug substance and product will employ the same environments and utilize existing plants that are also currently manufacturing other pharmaceutical products.

ENVIRONMENTAL ASSESSMENT

Ropinirole (SK&F 101468) Tablets

NDA 20-658

4.3. Locations where Drug Substance will be Produced

Ropinirole, the drug substance in the product which is the subject of the proposed action, is manufactured in 5 process stages.

The drug substance manufacturing facilities are described below; Worthing is considered to be an alternate manufacturing site.

4.3.1. Cork, Ireland

SmithKline Beecham (Manufacturing) Limited
Currabinny
Carrigaline
County Cork
Ireland

SmithKline Beecham (Manufacturing) Limited, Cork (Ireland) is located approximately twelve miles south of Cork City on the southern shores of Cork Harbor. There is a total landbank of 130 acres, but the facility occupies only 28 acres. The immediate area is rural, with some farms and dwellings within a half mile radius of the boundary fence. The site discharges an aqueous waste into Cork Harbor after on-site biological treatment.

4.3.2. Worthing, U.K.

SmithKline Beecham Pharmaceuticals
Clarendon Road
Worthing
West Sussex BN14 8QH
United Kingdom

This facility is located on the south coast of England (U.K.), at the edge of an urban area, approximately one mile from the sea. The site is abutted by residential property on its northern boundary and light industrial installations to the West and South. Agricultural land borders to the east and northeast. The bedrock beneath the site consists of chalk, covered with a variable sequence of unconsolidated sediments, including clay strata. The site covers 37 acres of flatland, of which 7 acres is devoted to company recreational facilities.

ENVIRONMENTAL ASSESSMENT

Ropinirole (SK&F 101468) Tablets

NDA 20-658

4.4. Location where Drug Product will be Produced

4.4.1. Crawley, U.K.

Ropinirole drug product will be prepared at the following facility:

SmithKline Beecham Pharmaceuticals Co.
Magpie Wood
Manor Royal
Crawley
West Sussex RH10 2QJ
U.K.

The Crawley facility for ropinirole product manufacture is located in a light industrial area near the city of Crawley, England (U.K.).

4.5. Locations where Product will be Used

The subject of this Environmental Assessment is the use of ropinirole drug product in the United States of America. Predominant use is expected to coincide with areas of greatest population density.

4.6. Locations where Product will be Disposed of

Ropinirole drug product returned goods will be collected at the following site:

Division KENCO Group Inc.
1704 Mid Park Drive
Knoxville, Tennessee 37291

From this site, the materials will be shipped to the following licensed facilities for disposal (e.g., destruction by high temperature incineration).

SmithKline Beecham Pharmaceuticals
Bristol Industrial Park
Weaver Pike
Bristol, Tennessee 37620

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Ropinirole (SK&F 101468) Tablets

NDA 20-658

Ogden Martin Systems of Lake, Inc.
3830 Rogers Industrial Park Road
Okahumpka, Florida 34762

Documentation for these disposal facilities is provided in Appendix I.

5. DESCRIPTION OF CHEMICAL SUBSTANCE THAT IS THE SUBJECT OF THE PROPOSED ACTION:

Ropinirole drug substance is described below. The components used in the manufacture of the drug substance and their CAS registry numbers are listed in Confidential Tables 1 and 8 (for Cork and Worthing, respectively). The components (and their CAS registry numbers) used in the manufacture of the drug product (at Crawley) are listed in Confidential Table 15. The environmental fate and effects of ropinirole, which is considered to represent the "worst-case" scenario in terms of any potential for environmental impact (see Item 7), is described in Items 7 and 8 of this assessment.

5.1. Complete Nomenclature for Ropinirole:

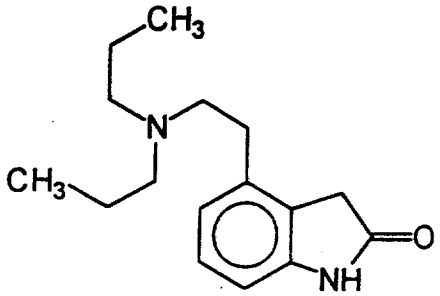
British Approved Name (BAN):	Ropinirole
Chemical Name:	4-[2-(N,N-dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one, monochloride
5.1.1. CAS Number:	91374-20-8
5.1.2. Laboratory Code:	SK&F 101468
5.1.3. Molecular Formula:	$C_{16}H_{24}N_2O$
5.1.4. Molecular Weight:	free base 260.38 g/mol, HCl salt 296.84 g/mol

ENVIRONMENTAL ASSESSMENT

Ropinirole (SK&F 101468) Tablets

NDA 20-658

5.1.5. Structural Formula:



5.1.6. Description:	White to pale greenish-yellow powder
5.1.7. Melting Point Range:	244.2-248.2 °C [1]
5.1.8. Additives:	Not applicable
5.1.9. Impurities:	

Organic impurities arising from the synthesis are determined by GC and HPLC. Solvent content is measured by GC and the inorganic impurities (heavy metals and sulfated ash) are also monitored. Identification is included on the drug substance specification. Ropinirole must be protected from direct sunlight; otherwise the compound is stable, and no degradants are likely to arise under normal storage conditions.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT:

6.1. Introduction from Production of Ropinirole

Ropinirole will be produced at SmithKline Beecham (Manufacturing) Limited, Cork, Ireland, as the principal drug substance manufacturing site. Ropinirole drug substance production may also be carried out at Worthing, a SmithKline Beecham Pharmaceuticals' facility in West Sussex, England (U.K.), which is considered to be an alternate manufacturing site. Ropinirole tablets will be made at SmithKline Beecham Pharmaceuticals' facility in Crawley, England (U.K.).

6.1.1. Introduction from Drug Substance Production at SmithKline Beecham (Manufacturing) Limited, Cork, Ireland

Ropinirole drug substance production will be carried out at SmithKline Beecham (Manufacturing) Limited, Cork, Ireland. All data tables for drug substance production at

Cork, Ireland, are presented in Confidential Attachment 3. Environmental evaluations of the impacts from drug substance production follow.

Ropinirole drug substance production will utilize the same facilities currently being used for the production of other pharmaceuticals. The following evaluations of the anticipated environmental impact of ropinirole production are based on estimates of maximum daily production and on existing waste treatment systems at SmithKline Beecham (Manufacturing) Limited, Cork, Ireland. Engineering estimates were used to predict anticipated discharge levels; however, the evaluations do not reflect changes in treatment process operations or technology which might be implemented before actual approval of this application.

SmithKline Beecham (Manufacturing) Limited, Cork, Ireland is expected to remain in compliance with applicable waste effluent permits throughout the production of ropinirole drug substance. The Cork facility is regulated under an Integrated Pollution Control (IPC) license (Reference Number in Register of Licenses: 4; Date of Notification: October 28, 1994), under authority of the Irish Environmental Protection Agency and the Environmental Protection Agency Act, 1992. This license contains permit levels and monitoring procedures for all plant emissions (wastewater, air, incinerators, etc.), as well as guidelines for the establishment of an Environment Management Programme, to assess all operations for the use of cleaner technology and the minimization of waste.

6.1.1.1. Waste Stream Summary and Disposition

The input chemicals (for overall production and per process stage) for ropinirole drug substance production are listed in Confidential Tables 1, 2A, 2B, 2C, 2D and 2E. Amounts and descriptions of wastes generated during ropinirole production are given in Confidential Tables 3, 4A, 4B, 4C, 4D and 4E. The waste streams generated at SmithKline Beecham (Manufacturing) Limited, Cork (Ireland) will be disposed of such that release into the environment (on-site and/or off-site disposal) will not exceed plant permit levels for the Cork facility (see Appendix II). The disposition of all ropinirole process waste streams is presented in Confidential Table 5.

6.1.1.2. Material Balance

Material balance information for the chemical inputs, process intermediates and effluents was determined, thus accounting for all materials and amounts used in or produced by the process. Waste outputs include leftover material resulting from production, and assay solutions sampled before and after filtration.

6.1.1.3. Controls Exercised on Wastes

6.1.1.3.1. Air and Off-Gases

The production site buildings at SmithKline Beecham (Manufacturing) Limited, Cork (Ireland) vent approximately 102,500 m^3 of air per hour. Air from the buildings where chemical processes are performed flows through two scrubbers. As it is discharged to the atmosphere, air is monitored by gas chromatography (and other methods) for several compounds. Fugitive emissions are monitored if there is reason to suspect a gaseous leak.

6.1.1.3.2. Incinerated Wastes

All aqueous waste streams and several solvent wastes resulting from ropinirole production at Cork will be incinerated either on or off site. There are three high-temperature natural-gas fired incinerators on site: two caloric down-fired units, and one hygrotherm horizontal unit. Only those wastes arising from the manufacture on-site of pharmaceutical active ingredients and intermediates shall be incinerated on-site. The manufacturing wastes to be incinerated may be organic solvents and residues from production operations, aqueous wastes contaminated with solvents, salts and residues, or gas streams containing organic and inorganic gases or contaminated air.

At discharge, gases from the plant's incinerators are continuously monitored for CO and total organic carbon (TOC). Individual incinerators are also monitored for sulphur dioxide (SO_2) or hydrochloric acid (HCL). The amount of organic material remaining after incineration is calculated using a 99.999% incineration destruction efficiency, based upon the known removal efficiencies for mercaptan and methylethyl ketone (MEK). The incinerators emissions are scrubbed with a caustic scrubber (assuming 99.9% efficiency) and the scrubber liquor is sent to the biotreatment facility. Liquid process effluents are usually stored prior to incineration.

Review of the measured and calculated levels of affected incineration effluent components, and a comparison with their permitted levels resulted in the determination that the Cork facility will be in compliance with their incinerator permits during the disposal of incinerated waste streams produced by ropinirole production (see Confidential Table 7). A summary of the ropinirole incinerated process effluent streams is presented in Confidential Table 6.

6.1.1.3.3. Solvent Recovery

Several waste streams from ropinirole production will be sent off-site for recovery of solvents (see Confidential Table 5). All foul organic solvents from the ropinirole production are expected to be disposed of to the foul solvent tanks for either recovery or off-site disposal through an audited contractor. All SB disposal contractors are audited by SmithKline Beecham.

6.1.1.3.4. Biotreatment System

None of the waste streams from the ropinirole process will be directly treated in the on-site wastewater biotreatment facility (see Confidential Table 5 in Confidential Attachment 3). The incinerator caustic scrubber liquor is usually treated in the on-site biotreatment facility.

The biotreatment facility incorporates a 3000 m^3 basin of activated sludge, which has a retention time of approximately 10 days. The waste to be biotreated (including sanitary effluents, floor washes, incinerator quench streams, scrubber liquor, and environmental spent liquors) is sent to an equalization tank prior to neutralization in a second tank. The wastes are then sent to the aeration basin. After aeration, the waste is sent to a clarifier. The clarifier is dosed with polyelectrolytes, and effluent wastes are sent to the final holding tank (300 m^3) prior to discharge. The treated liquid effluent is disposed of via pipeline into Cork Harbour. The sludge generated at the biotreatment plant is mechanically dewatered prior to off-site disposal to a landfill.

Several parameters of the effluent are monitored on a continuous or daily basis, such as inlet and outlet flows, pH, TDS and COD. The levels of several metals are also monitored, on a monthly or annual basis.

6.1.1.3.5. Solid Waste

One waste stream from ropinirole production will be sent off-site for recovery of the catalyst (see Confidential Table 5). There are currently no limits as to the amount of solid wastes disposed of off-site. All SB disposal contractors are audited by SmithKline Beecham.

6.1.1.4. Certification of Compliance

SmithKline Beecham (Manufacturing) Limited, Cork (Ireland) is committed to environmental control and will operate within its permits during ropinirole drug substance production. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix II.

6.1.2. Ropinirole (Drug Substance) Production at Worthing

Ropinirole may also be produced at Worthing, a SmithKline Beecham Pharmaceuticals' facility in West Sussex, England (U.K.). Worthing is an alternate manufacturing site for ropinirole. The following evaluation of the anticipated environmental impact of ropinirole production is based on expected production levels and existing waste treatment systems at this facility. Confidential Tables relating to ropinirole drug substance production at Worthing are presented in Confidential Attachment 4. The chemicals that would be used at Worthing for ropinirole production are listed in Confidential Table 8, and the quantities expected to be used during each stage are presented in Confidential Tables 9A, 9B, 9C, 9D and 9E.

Bulk drug substance produced at Worthing is stored at ambient temperature in double plastic lined plastic drums. The drums are well-labeled as to the status of the contents. Various grades of material are segregated in storage, and their release is authorized by the Analytical Sciences Development Manager or the Quality Assurance Manager. Environmental evaluations of the impacts from ropinirole production follow.

6.1.2.1. Waste Stream Summary and Disposition

A list of effluent chemicals is presented in Confidential Table 10, and their amounts are presented in Confidential Tables 11A, 11B, 11C, 11D and 11E. A description of the waste stream disposal destinations is found in Confidential Table 12. In compliance with the "Control of Substances Hazardous to Health" regulations, prior assessment of all chemical processes is made. Operating procedures are such that any exposure to chemicals is minimized. Where exposure to chemicals cannot be prevented, the use of local exhaust ventilation and personal protection equipment ensures adequate personal protection. Health and environmental monitoring are carried out as required.

At the Worthing site, process waste is handled in such a manner as to meet permitted site discharge levels. Based on the controlled disposition of wastes from production at Worthing, no chemicals should be discharged into the environment at levels greater than the mass limits or concentration limits as set by Her Majesty's Inspectorate of Pollution (HMIP) in the relevant process authorization.

6.1.2.2. Material Balance

Material balance information for the chemical inputs, process intermediates and effluents was determined for the production of drug substance, taking into account all materials and amounts used in or produced by the process. Waste outputs include leftover material resulting from production and assay solutions sampled before and after filtration. The disposition of all waste streams produced during ropinirole production is presented in Confidential Table 12.

6.1.2.3. Controls Exercised on Wastes

6.1.2.3.1. Gaseous Waste

At Worthing, all reactions are carried out under closed systems wherever possible to minimize gaseous waste. All reactor outlets are scrubbed as necessary. The Worthing facility is required to minimize production gaseous emissions in accordance with their process authorizations as granted by HMIP, received March, 1994.

6.1.2.3.2. Solvent Waste Recovery and Disposal

Foul solvent waste streams produced during ropinirole drug substance production not suitable for aqueous discharge would be disposed of to foul solvent tanks, for either recovery or off-site disposal through an audited contractor. Several solvent streams would be recovered during production at Worthing.

6.1.2.3.3. Aqueous Waste Recovery and Disposal

Solvent from one aqueous waste stream would be recovered, while most aqueous waste streams are expected to be sent off site for disposal. Some of the aqueous waste streams produced during ropinirole drug substance production (see Confidential Table 12) would be combined and released with the site effluent. The aqueous waste is first cooled to ambient temperature and adjusted to pH 7-9 before being discharged to site effluent, and in some cases, where necessary, it is extracted with organic solvent prior to discharge.

Process waste is appropriately handled in order to meet permitted site discharge levels. Waste stream effluent from the site as a whole must not exceed the Consent Conditions granted by the National Rivers Authority (NRA), which governs the facility's discharge limits to controlled waters.

The components of the aqueous process waste streams and their calculated quantities are summarized in Confidential Table 13; their process contributions to the effluent were calculated by mass balance around the ropinirole process. Also, Chemical Oxygen Demand (COD) contributions to effluent were measured directly; samples of actual waste streams from pilot scale production were obtained and analyzed for COD concentration. The measured COD stream concentrations and the expected overall contribution to the effluent are also presented in Table 13. The major regulated components in the aqueous waste are summarized in Confidential Table 14, and their concentrations in the effluent were compared with current permit levels. For developing the discharge level data, it is assumed that no volatilization, biodegradation or adsorption of the materials occurs. Review of the measured and calculated concentrations of affected aqueous effluent components, and a comparison with their permitted limits resulted in the determination that the Worthing facility would be in compliance with its aqueous effluent permits during ropinirole substance production.

The consent conditions (permit levels) and a citation of and statement of compliance with applicable emissions requirements are presented in Appendix III.

6.1.2.3.4. Solid Wastes

A catalyst used in the process would be recovered from one ropinirole waste stream. Solid waste produced during the ropinirole production process would be disposed of by an off-site licensed hazardous waste disposal company. Non-hazardous solid waste, such as celite, silica and charcoal, is classified as industrial waste under the Controlled Waste Regulations 1992. Disposal of such waste is regulated by the appropriate Waste Disposal Authority, and sent for disposal to a licensed landfill site. All SB disposal contractors are audited by SmithKline Beecham, and prior to the removal of wastes from the Worthing plant, documents ensuring good disposal practices are filed with the disposal company.

SmithKline Beecham Pharmaceuticals (Worthing) is committed to environmental control and will operate within its permit levels during the production of ropinirole drug substance.

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6.1.2.3.5. Environmental Legislation

The main piece of legislation governing the disposition of wastes from production is the Environmental Protection Act 1990 ("the 1990 Act"). In addition, listed in Appendix VI are the statutory instruments for the United Kingdom that are applicable to the Worthing site and the production of ropinirole drug substance.

6.1.2.4. Safety Considerations

Operating procedures were established to minimize personnel exposure to chemicals, including the use of local exhaust ventilation and personal protective equipment. Health and environmental monitoring procedures are performed as required.

6.1.2.5. Emergency Response Plan

If the fire alarm or toxic gas alarm is activated, the Plant Supervisor assumes the role of Incident Controller and will evacuate the area, if required. The Site Control Center will be alerted, which in turn summons the Fire Brigades.

Plant personnel are trained in emergency response measures, and if necessary will re-enter the area wearing protective clothing and breathing apparatus to take immediate remedial action.

The fire alarm automatically initiates a response from the external fire brigade. The first arrival of the fire brigade occurs approximately 4 minutes after the alarm is sounded, with additional firemen assisting in accordance with the external emergency service response plan for the Worthing site.

In emergencies, communications are coordinated at the main gatehouse, which is continuously manned by security personnel. Communication systems include radio communications to each site area, a site-wide personnel address system, and emergency telephones.

Emergency equipment immediately available to the Incident Controller and his staff includes fire hoses, fire extinguishers, water monitors, breathing apparatus, and protective clothing.

In the event of a serious escalation of an emergency situation, the major emergency plan for the site will be implemented, which results in mobilization of senior managers and technical specialists.

6.1.2.6. Spill Control

All storage vessels are contained within spillage bunds (dikes), in accordance with Health and Safety Executive guidelines on the storage of flammable liquids and other materials.

All production plant and material storage areas are served by the site effluent drainage system, which directs waste waters to the sea outfall. Consequently, spills in these areas are prevented from entering local surface waters.

Any minor spills in production areas are handled by process staff, following appropriate spill procedures described for each type of material. Larger spills may either be retained in storage tank bunds, or otherwise drained to the site effluent system with waste water. The first action by process staff is to shut off the source of the spill, if possible, and alert supervisory staff and the Incident Control Team.

The Incident Control Team will use spill booms and absorbents to contain spilled material as much as possible, and then pump it into suitable containers. If necessary, substantial quantities of material that enter the site effluent system can be intercepted before release by holding the effluent in one of the balance/equalization tanks at the effluent outfall, where it may be treated appropriately.

If a spill occurs outside the areas served by the site effluent system, (e.g., during transport on site), storm water outfalls can be plugged to limit the movement of material to surface water courses outside the site boundary, in addition to the Incident Control Team's efforts to contain the spill.

6.1.2.7. Certification of Compliance

SmithKline Beecham Pharmaceuticals, Worthing, England, (U.K.), should the site be used to manufacture ropinirole drug substance, will operate within its permits. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix III.

6.1.3. Introduction from Production of Drug Product at Crawley

Ropinirole tablets will be produced in one process stage, consisting of granulation, compression, coating and packaging at SmithKline Beecham Pharmaceuticals' facility in Crawley, England (U.K.). In compliance with the U.K. "Control of Substances Hazardous to Health" regulations, assessment of all chemical processes is made prior to initiation of production. The manufacture of ropinirole drug product will employ the same environment

and utilize the existing plants that are currently used to manufacture other pharmaceutical products. Ropinirole will be prepared as 0.25, 0.5, 1.0, 2.0 and 5.0 mg tablets.

For the purposes of this assessment, material balance tables for the production of only the 0.25 mg tablets are included, with those calculations performed under the assumption that all ropinirole drug substance projected to be required would be made into 0.25 mg tablets. These tables, for production of 0.25 mg tablets, are given in Confidential Attachment 5. In terms of waste amounts produced during production, this represents a "worst case" scenario: at an assumed loss of 3% of the components used to make the tablets, an assessment can be made of potential "worst case" impacts during production from the disposal of those components. Environmental evaluations of the impacts from drug product production follow.

6.1.3.1. Waste Stream Summary and Disposition

The disposition and total "worst case" quantities of waste generated during ropinirole 0.25 mg tablets production are given in Confidential Tables 17 and 18. The waste streams generated at the Crawley facility will be disposed of using appropriate procedures, such that release into the environment (as aqueous waste, considering a 3% loss to equipment and floor washings) is not expected to exceed Crawley aqueous waste permit levels. All waste disposal contractors are audited by SmithKline Beecham Pharmaceuticals at Crawley.

6.1.3.2. Material Balance

Material balance information for one lot of chemical inputs and effluents was determined, thus accounting for all materials and amounts expected to be used in or produced during the drug product process. Waste outputs include leftover material resulting from production, inspection operations (rejects are discarded), assay materials sampled, and floor and equipment washings.

6.1.3.3. Controls Exercised on Wastes

The main piece of legislation governing the disposition of aqueous waste from the ropinirole tablet production is The Water Industry Act 1991.

6.1.3.3.1. Aqueous Wastes

Since ropinirole is very water soluble, all tableting equipment will be washed with soap and water. Coating machinery does not become heavily soiled with drug substance, and will also be washed down with soap and water. This dilute aqueous waste will be disposed of

through the site aqueous effluent. All aqueous wastestreams go to a publicly owned treatment works. The effluent discharged from the SmithKline Beecham plant at Crawley has to meet certain waste treatment parameter criteria. These parameters are monitored internally by SmithKline Beecham Quality Control and externally by the regulatory agency without prior notice. At present, all the generated aqueous waste is stored in two tanks (2500 liter capacity) outside the building and disposed of off-site when the tanks are full.

The projected "worst case" Chemical Oxygen Demand (COD) and Total Suspended Solids (TSS) concentrations and a comparison with their permitted levels are presented in Confidential Table 19. For the purposes of this evaluation, the production campaign is assumed to use all of the drug product, which is based on the 5th year projected production of ropinirole.

Review of the calculated concentrations of affected aqueous effluent components and a comparison with their permit levels resulted in the determination that the Crawley facility would be in compliance with their aqueous effluent limits under the worst case production scenario described. Thus, under conditions of actual production, where lesser amounts of the tableting components will be used to make higher-strength tablets, the quality of the effluent discharge should meet the United Kingdom's water quality standards.

6.1.3.4. Environmental Legislation

Presented in Appendix VI are the regulations for the United Kingdom that are applicable to the Crawley site and the production of ropinirole tablets, as well as the Worthing and Cork sites for the production of ropinirole drug substance.

6.1.3.5. Safety

The Crawley facility operates to site and departmental emergency procedures. Plant operators are trained under an established training plan, and a personal training record is maintained for each operator.

Disposable protective overalls, overshoes, hats and gloves together with appropriate dust respirators are worn by plant personnel when handling individual batch materials, intermediates and finished products. Care is taken to avoid creating excessive dust, and local exhaust ventilation is used at points of activity, such as loading, unloading and transferring materials. Appropriate Standard Operating Procedures are followed for the use and cleaning of equipment and manufacturing areas.

A procedure for cleaning spills is included in the operating instructions. Due to the relatively small quantities of materials involved, there are no containment dikes or other spill control devices to contain potential spills. In the event of a spill, as much of the spilled material is collected as practicable and weighed for reconciliation purposes. The material is then disposed of using methods described in its Material Hazard sheet. Powder spills are cleaned using a Type H dedicated vacuum cleaner, and the collected material is disposed of by the same route as other solid waste materials.

6.1.3.6. Certification of Compliance

SmithKline Beecham Pharmaceuticals, Crawley, England (U.K.), will operate within its permits during the production of ropinirole tablets. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix IV. A Material Safety Data Sheet for ropinirole and a summary of its environmental fate and effects data are given in Appendix V.

6.2. Introduction from Use of Drug Product

Human pharmacokinetic studies indicate that adsorption and metabolism of ropinirole is extensive, with most of the administered ropinirole expected to be excreted rapidly, primarilty as metabolites [2] (see Item 7.1 for additional details). However, for the purposes of this assessment, it is assumed that 100% of the applied ropinirole dosage will be excreted into the environment as unchanged ropinirole. This may be taken as a "worst case" scenario, since a comparison of toxicity estimates indicates that metabolite toxicities would be expected to be equal to or less than ropinirole itself, and since the metabolites exhibit a reduced potential for bioconcentration and bioaccumulation (see Item 7.1.1 for details).

Estimates of the Maximum Expected Emitted Concentrations (MEEC) and the Predicted Environmental Concentrations (PEC) of ropinirole from use of Ropinirole Tablets is given in Confidential Attachment 7. Analyses of the fate and effects of ropinirole (and its metabolites) are presented in Item 7 and Item 8, respectively, of this assessment.

6.3. Introduction from Disposal of Drug Product

Ropinirole drug product returned goods will be collected at the following site:

Division KENCO Group Inc.
1704 Mid Park Drive
Knoxville, Tennessee 37291

From this site, the materials will be shipped to the following licensed facilities for disposal (e.g., destruction by high temperature incineration).

SmithKline Beecham Pharmaceuticals
Bristol Industrial Park
Weaver Pike
Bristol, Tennessee 37620

Ogden Martin Systems of Lake, Inc.
3830 Rogers Industrial Park Road
Okahumpka, Florida 34762

Documentation for these disposal facilities is provided in Appendix I. Based on the controlled and highly efficient thermal destruction of unused ropinirole drug substance and product, no material should be introduced into the environment from disposal.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

7.1. Metabolism

The metabolism of SK&F 101468 was determined using ^{14}C-SK&F 101468 in four human subjects as two doses separated by at least 28 days [2]. Excretion of ^{14}C was rapid and essentially complete (by 192 hours) following both intravenous and oral dosing. Most of the ^{14}C activity (~90% of the doses) was excreted in urine. Metabolism was extensive, and a putative metabolic pathway was identified (Figure 1). Those compounds determined to be excreted at ~10% or more of the administered dose are shown in Figure 2.

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Figure 1. Putative Metabolic Pathway of Ropinirole in Humans.

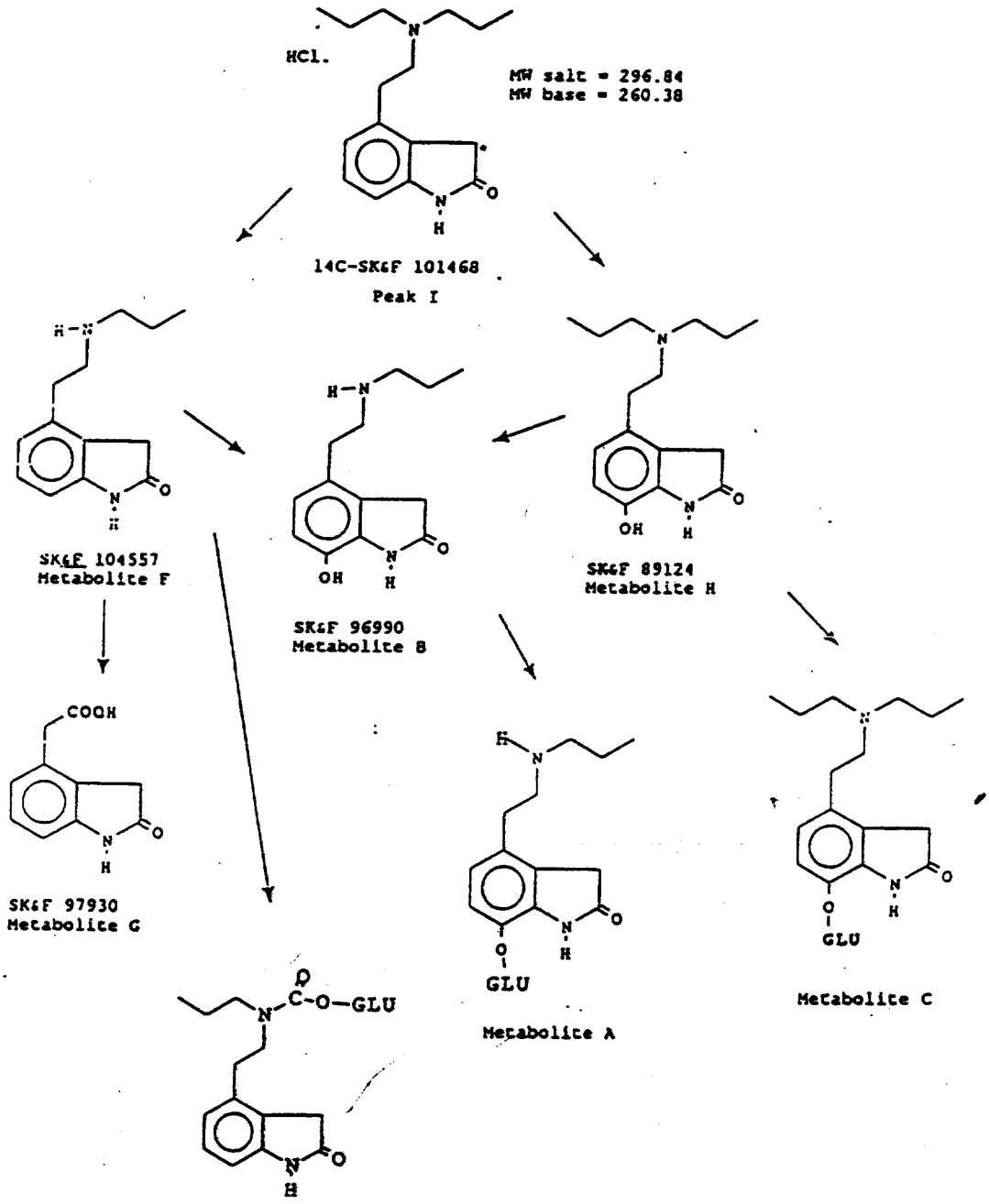
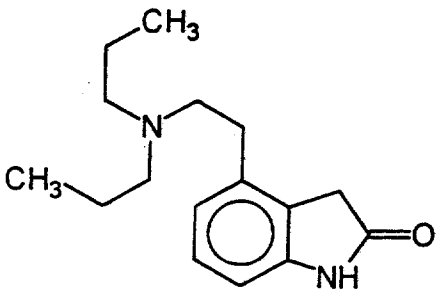
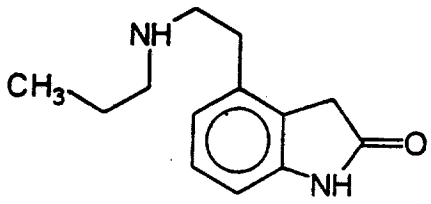


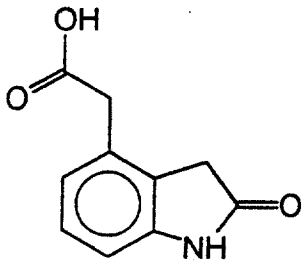
Figure 2. Major Human Excretion Products.



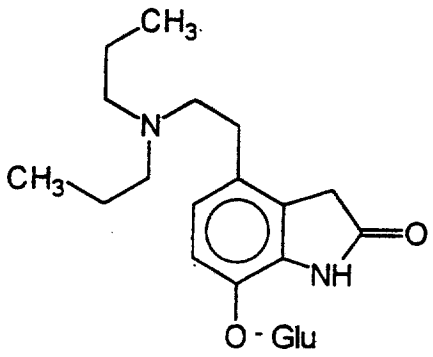
SK&F 101468 (parent) (~10%)



SK&F 104557 (~32-45%)



SK&F 097930 (~10%)



SK&F 089124 glucuronide (~10%

7.1.1. Evaluation of Metabolites

SK&F 89124 is excreted as the glucuronide conjugate but is expected to be rapidly converted to the hydroxyl form in the aquatic environment. All three of the major metabolites are structurally similar to ropinirole, but would be expected to be more hydrophilic. A comparison of estimated key physical properties, lipophilic partitioning properties and aquatic toxicity is given in the table below.

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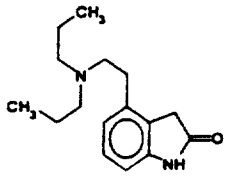
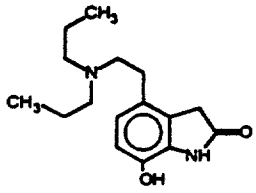
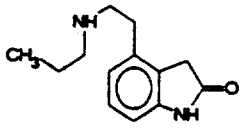
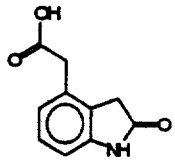
	Ropinirole	SK&F 89124	SK&F 104557	SK&F 97930
				
Molecular Weight	260.38	276.38	218.3	191.2
Log P[1]	2.51	1.84	1.28	0.21
Water Solubility (g/L)[2]	0.47	1.29	8.89	93.6
pKa[2]	10.2*	9.92*	10.98*	4.3**
Log K_{oc}[2]	2.74	2.38	2.07	1.49
Log BCF[2]	1.58	1.05	0.61	-0.23
TopKAT[3] Aquatic Toxicity Estimate (Fat Head Minnow EC50)	91 mg/L	82 mg/L	211 mg/L	88 mg/L

1 calculated using ClogP [3]
2 calculated using QSAR [4]
3 estimated using TOPKAT [5]
* refers to amine functional group
** refers to carboxylic acid functional group

The calculated properties for ropinirole presented in the table are generally in good agreement with the respective experimentally determined values presented in the following sections. This agreement serves as a basis and justification for conducting a predictive property comparison between the metabolites and the parent.

Log P_{ow} is the critical parameter for evaluating lipophilic partitioning behavior between different environment compartments. Compared to ropinirole, all the predicted log P_{ow}'s for metabolites are significantly lower, indicating a reduced potential for bioconcentration and bioaccumulation. The presence of ionizable functional groups in ropinirole and the metabolites results in distribution coefficient (D_{ow}) values which would be expected to be 2 to 3 log units below the corresponding P_{ow} coefficients over typical environmental pH ranges.

This further minimizes and drastically reduces the metabolites' potential for bioconcentration and bioaccumulation in the aquatic compartment.

Aquatic toxicity estimates are presented in the table above for ropinirole and its three major metabolites. The estimate for ropinirole is in good agreement with the mean of three experimentally derived aquatic value (91 mg/L (estimated) as compared to 27 mg/L (experimental)). Comparison of the estimates indicates that metabolite toxicities would be expected to be equal to or less than ropinirole itself.

Thus, an evaluation of the data above indicates that environmental fate and effects studies should be performed on the "worst-case" compound, ropinirole. Consequently, no studies were conducted on its metabolites.

7.2. Physical Properties of Ropinirole

The following physical properties were determined for ropinirole. Details are provided in the following sections.

Property	Value	Comment
Dissociation Constants (basic)	pK_1~9.6, pK_2~12.0	see 7.2.1
Aqueous Solubility	133000 mg/L	see 7.2.2
Octanol/water Distribution Coefficient	log D_{ow}= 0.507 @ pH 6.9	see 7.2.3
Henry's Law Constant	<5.69E-7 $m^3 \cdot atm/mol$	see 7.2.4
Sludge Adsorption	K_p 83.2 mL/g, log K_p 1.92	see 7.2.5
UV/vis Spectrum	λ_{max} at 210 and 250 nm log ε_λ = 3.94 to 4.30 $M^{-1} \cdot cm^{-1}$ cutoff at ~300 nm	see 7.2.6

7.2.1. Dissociation Constants

Two separate determinations indicate that ropinirole has two basic pK_a values.

reference	pK_1 (tertiary amine)	pK_2 (indole N)
[1]	9.5	11.6
[6]	9.68	12.43

In aqueous solution, ropinirole will exist primarily as the dicationic species across the typical range of environmental pH values (5<pH<9). Only a very small fraction of dissolved ropinirole molecules will exist as the free base species in the pH range of 5 to 9.

7.2.2. Aqueous Solubility

Solubility data for ropinirole are summarized below [1].

Solvent	Solubility (mg/L)
Water [a]	133,000
0.1 M HCl	86,900
0.1 N NaOH	>3,700
EtOH	4,200
Methylene chloride	300

[a] pH not specified

The solubility data indicate that ropinirole hydrochloride is extremely soluble in protic solvents. Since ropinirole is a base, the aqueous solubility is expected to be lowest at high pH. The solubility data for 0.1 N NaOH above in all probability approximates the minimum aqueous solubility for ropinirole.

7.2.3. Octanol/Water Distribution and Partition Coefficients (Dow and Pow)

Ropinirole, a base with reported pK_a values of 9.68 and 12.43, exists primarily as the cationic species throughout the environmentally relevant pH range of 5 to 9. Therefore, octanol/water distribution coefficients (D_{ow}) of ^{14}C-ropinirole were determined at pH 4.9, 6.9, 9.1, and 11.5 using shake-flask methodology [7]. The experimental data are summarized below.

pH	Mean D_{ow}	st. dev.	Log mean D_{ow}	Calculated log mean P_{ow}*
4.9	0.117	0.0061	-0.93	3.85
6.9	3.21	0.074	0.507	3.28
9.1	119	4.79	2.08	2.73
11.5	134	2.22	2.13	2.13

* $\log P_{ow} = \log D_{ow} + \log (1 + 10^{pKa-pH})$

As expected for a base, D_{ow} varied considerably as a function of aqueous phase pH. For the pH 4.9, 6.9, and 9.1 data, log D_{ow} showed a strong linear correlation with aqueous phase pH:

$$\log D_{ow} = 0.709pH - 4.4012, \quad r^2=0.9998$$

During a separate experiment using shake flask methodology, the log D_{ow} of non-labeled ropinirole was directly determined to be 2.33 at pH 8.43 [6]. Both studies indicate that at a typical environmental pH of ~7, ropinirole exists primarily as an ionized species that is unlikely to bioconcentrate or bioaccumulate.

The calculated P_{ow} values should be independent of pH as it is only concerned with, by definition, partitioning of the unionized species - the free base form of ropinirole. The calculated values shown above are obviously not independent of pH. The dependency is most likely due to the formation of neutral ion pairs composed of a protonated ropinirole cation and a buffer counter anion. This argument is consistent with the convergence of D_{ow} and P_{ow} values at pH 11.5, where the unionized free base predominates.

7.2.4. Henry's Law Constant

An experimental determination of the Henry's law constant (H_L) of ^{14}C-ropinirole yielded a value of 5.69E-7 m^3·atm/mol [8]. However, the slope of the first-order volatilization plot (ln C/C_o versus time) of the experimental data was not significantly different from zero at the 95% confidence level. These data suggest that volatilization of ropinirole will be an insignificant transport mechanism in the environment.

7.2.5. Activated Sludge Adsorption

Two experiments were conducted to determine the rate and extent of adsorption of ^{14}C-ropinirole to lyophilized activated sludge solids [9]. During the preliminary rate experiment, adsorption equilibrium was attained within 2.4 hours of contact; the mean sludge/water distribution ratio (K_d) was 55.7 $\pm$ 12.6.

A definitive isotherm determination was subsequently conducted. The initial sludge total suspended solids concentration (TSS) was 2290 mg/L and initial ^{14}C-ropinirole concentrations ranged from 10.9 to 1110 ug/L. The resulting Freundlich isotherm had a high degree of linearity ($r^2 = 0.989$) and a slope of near unity (1/n = 0.987), indicating that K_d was independent of ^{14}C-ropinirole concentration. The Freundlich isotherm constant (log K) was 1.92 (K = 83.2).

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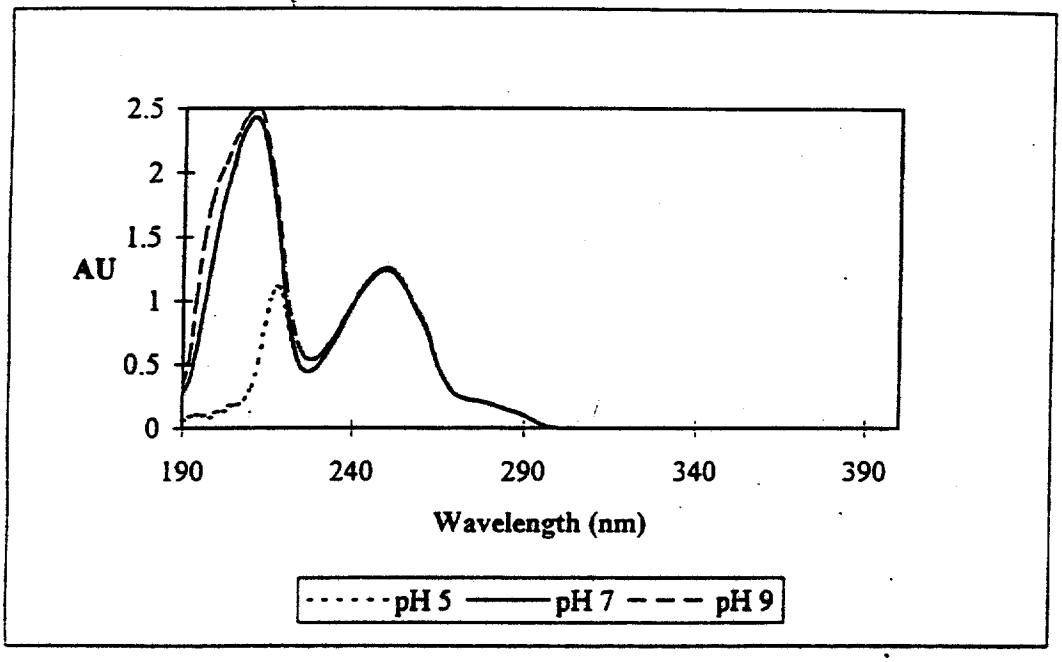
7.2.6. UV/vis Spectrum

UV/vis spectra of ropinirole (32.9 mg/L or 1.26E-4 M) were determined in pH 5, 7, and 9 buffers [10]. At wavelengths above 230 nm, the spectra did not change as a function of pH. The UV/vis cutoff was ~300 nm.



Absorption maxima and extinction coefficients are shown below.

pH	Wavelength (nm)	Extinction Coefficient ($M^{-1}\cdot cm^{-1}$)
5	218	8780
5	250	9910
7	210	19270
7	250	9840
9	210	19730
9	250	9970

7.3. Transformation and Depletion Mechanisms

A description of the analytical method used to support fate studies performed at the Environmental Research Laboratory is given in reference [11].

7.3.1. Microbial Biodegradation

Several studies were initiated to examine potential ropinirole biodegradation in activated sludge wastewater matrices. Results of one study to determine the rate and extent of cometabolic mineralization of ropinirole may be found in reference [12]. The following studies were also conducted, and are summarized in reference [13]:

Study Description	ERL Study No.
Batch Activated Sludge (BAS)	94-006
Semi-Continuous Activated Sludge (SCAS)	94-018
SCAS w/ ropinirole-acclimated inoculum	94-019
Continuous Activated Sludge (CAS)	94-022
SCAS w/ indoline-acclimated inoculum	95-006

In all cases no significant ropinirole degradation was observed in any of the studies conducted. Degradants attributed to biotic activity were observed in the BAS and SCAS test systems; however, no major reductions (> 15-20%) in ropinirole solution concentration were observed in either of these studies [13].

The CAS study utilized a flow-through system that mimicked the operational parameters of a full-scale wastewater treatment plant (WWTP). The system was operational for over seven weeks and was fed actual primary effluent from a local WWTP. No appreciable ropinirole degradation or metabolite formation was observed, even at extended hydraulic retention times.

No evidence of any significant biodegradation was observed during the studies conducted and microbial inhibition did not appear to be a contributing factor, since ropinirole microbial inhibition concentrations appear to be in excess of 500 mg/L. This lack of biodegradation is probably attributable in some part to the protonated tertiary amine group present on the side chain of ropinirole, since the other functional moieties of the molecule should be susceptible to monooxygenase-induced biotransformation resulting in more polar biologically-degradable products.

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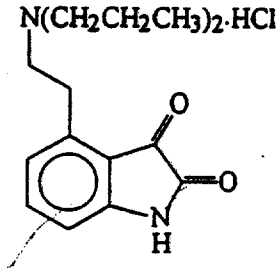
7.3.2. Algal Biodegradation

Based upon analytical chemistry assay data that detected at least 7 potential algal biotransformation products from the acute algal toxicity study that was conducted [14], an additional study was conducted to further examine ropinirole biotransformation potential by the green algae *Selenastrum capricornutum* [15]. This study included test compound exposure, biological control, and chemical control flasks. All vessels were exposed to ambient sunlight and temperature and the ropinirole starting nominal concentration was 30 mg/L.

The results of study 95-008 [15] indicated that ropinirole slowly degraded during the 29 days of the study and several degradants were observed. Quantitative results at a 30 mg/L ropinirole concentration were used to calculate a first-order rate constant of 0.032 day^{-1} and a half-life of 21.7 days. However, a comparison of kinetics data developed from both studies indicated a rate constant dependence on ropinirole concentration. Having established an algal EC50 of 33.4 mg/L, it is most likely that the rate constant dependence involved inhibitory effects. Therefore, kinetic analysis of rate data generated below the inhibitory concentration would be more representative of environmental scenarios. For a 10 mg/L starting concentration the first-order rate constant and half-life were determined to be 0.085 (day^{-1}) and 8.2 days, respectively. Algal degradation appears to be a significant depletion mechanism in the aquatic environment.

Of the multiple degradant products detected, two were tentatively identified by matching the UV spectra and retention times with those of authentic reference standards. Based upon these data, these two algal degradants were identified as SK&F 104557A (see Section 7.1) and SK&F 96266A (shown below). Additional LC/MS analyses confirmed the compound identifications [16].



SK&F 96266A

7.3.3. Direct Sunlight Photolysis

An experiment was conducted to determine the direct sunlight photolysis kinetics of ropinirole [10, 17]. Solutions of ropinirole (16.0 mg/L in deionized water) were exposed to ambient sunlight for up to 6 days, from 31 May 1995 to 6 June 1995 in Swedeland, PA (~40 °N latitude). The concentrations of ropinirole in samples of the photo-exposed solutions were determined by HPLC. Concentration data were converted to natural logarithms (ln) and plotted as a function of time in hours. The first-order photolysis rate constant (k, the negative slope of the least squares linear line) was determined to be 6.66E-4 hr^{-1}. The corresponding photolysis half-life ($t_{1/2}$=0.693/k) was 1040 hours. However, a *t*-test for significance of slope indicated that the slope of the linear regression line was not significantly different from zero at the 95% confidence level. Therefore, direct aquatic photolysis is not be expected to be a major depletion mechanism.

However, comparison of chemical control samples at pH ~7 from long-term microbial and algal degradation studies indicate that there appears to be a slow photooxidation of ropinirole in aqueous solution [15]. The major degradation products are SK&F 104557 (see Section 7.1) and SK&F 96266 (see section 7.3.2). Although not a major depletion mechanism, aqueous photooxidation could potentially mitigate ropinirole persistence in the aquatic compartment.

7.3.4. Hydrolytic Stability

In aqueous solution under darkened storage conditions, ropinirole hydrolytic stability appears to be inversely related to pH. The following table presents data on the degradation of 2 mg/mL solutions of SK&F 101468, stored at 85 °C for 4 days [1].

Initial pH	% of Initial SK&F 101468 Remaining
3.00	101.5
4.28	92.9
5.45	69.5
6.30	40.9
7.51	11.3
8.98	5.7

The data can be used to estimate first-order hydrolysis rate constants using the following equation.

$$-(\ln(C/C_o))/t = k$$

where:

C = concentration of ropinirole at time t
C_o = initial concentration of ropinirole at time zero
k = first-order hydrolysis rate constant ($time^{-1}$)

For the pH 7.51 data, $C_o = 1.00$, $C = 0.113$, $t = 4$ days, and therefore, $k = 0.545\ day^{-1}$ at 85°C. An estimated rate constant at 15°C of 4.26E-3 day^{-1} ($t_{1/2}$ = 163 days) was obtained by assuming that the rate constant decreased by a factor of two for every 10°C decrease in temperature.

7.4 Summary - Predicted Environmental Fate of Ropinirole in the Environment

Experimental data obtained for ropinirole suggest that ropinirole will not be significantly depleted by biodegradation or direct photolysis in wastewater treatment plants (WWTPs) or the ambient environment. Ropinirole entering WWTPs is expected to distribute between the aqueous and solid (activated sludge solids) phases. Assuming that the Freundlich isotherm constant of 83.2 represents a best estimate of the sludge/water distribution coefficient (K_p), the fraction of ropinirole expected to adsorb may be calculated using the following equation.

$$F_s = (K_p \cdot F_{tss})/(1+(K_p \cdot F_{tss}))$$

where:

F_s = fraction adsorbed
K_p = distribution coefficient (83.2)
F_{tss} = weight fraction of suspended solids

In the U.S., approximately 3.1E13 L/yr of wastewater and 5.9E9 kg/yr of waste activated sludge solids are produced [18]. The resulting solids to wastewater ratio is 1.59E-4 kg/L. Using this value as F_{tss} in the above equation, F_s equals 0.013 or 1.3 percent. Therefore, assuming no depletion, ~1.3 % of the ropinirole entering a WWTP is expected to adsorb to activated sludge solids and ~98.7 % is expected to enter receiving waters via WWTP effluent. Ropinirole that enters the aquatic environment is expected to be subject to algal degradation, aqueous photooxidation and slow hydrolysis. This may be taken as the "worst-case" scenario, since ropinirole is expected to represent only ~ 10% of the total excreted dosages. Since the three major metabolites are structurally similar to ropinirole, but are expected to be more hydrophilic, they would be expected to partition extensively to the aqueous phase in a WWTP. In addition, it is predicted that the toxicity of the metabolites would to be equal to or less than ropinirole itself.

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8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

8.1. Human and Mammalian Health Effects Summary

8.1.1. Acute Toxicity Studies

8.1.1.1. Oral Toxicity [19]

The oral acute toxicity of ropinirole has been examined in the mouse and in the rat. The oral LD_{50} values were 983 mg/kg for rats and 749 mg/kg for mice. Ropinirole exhibited moderate toxicity following a single, oral treatment.

8.1.1.2. Skin Irritation [19]

Ropinirole was classified as a mild irritant to rabbit skin. Redness occurred up to one day following direct application in rabbits for 4 hours. Skin appeared normal two days after treatment.

8.1.1.3. Eye Irritation [19]

Ropinirole was classified as a moderate irritant in rabbit eyes. Conjunctival redness, swelling and discharge, with iritis and corneal opacity occurred up to 3 days after direct application in rabbits. Eyes appeared normal 7 days after treatment. Water irrigation reduced irritation.

8.1.1.4. Sensitization [19]

Ropinirole was classified as a non-sensitizer to guinea pig skin. No adverse skin reactions or irritation occurred in guinea pigs used to test for allergic reaction or sensitization (maximization test).

8.1.2. Chronic Toxicity Studies [19]

8.1.2.1. Carcinogenicity

Ropinirole is listed as a animal carcinogen, according to SmithKline Beecham criteria (category 2). Substances classified as category 2 are positive in animal carcinogenicity studies by a mechanism not related to genetic damage and where a threshold is considered to exist. It is not listed as a carcinogen by IARC, NTP or US OSHA.

8.1.2.2. Reproduction toxicology

The rat and rabbit were used to assess the potential of ropinirole to cause embryo toxicity. These studies did not indicate any teratogenic effects in rabbits. In studies with rats, teratogenic effects occurred at dose levels significantly higher than human clinical doses. After birth, decreased pup growth also occurred, which was apparently related to impaired maternal lactation.

8.1.2.3. Mutagenicity studies

Ropinirole was determined to not be mutagenic in bacteria (Ames test) or other laboratory tests (*in vivo* cytogenetics, mouse lymphoma and mouse micronucleus tests).

8.2. Acute Aquatic Toxicity Studies

Acute aquatic toxicity studies with SK&F 101468-A were conducted on the water flea, *Daphnia magna*; a green algae, *Selenastrum capricornutum*; and the bluegill sunfish, *Lepomis macrochirus*. The analytical method validation study used to support the fish toxicity study is given in reference [20]. A description of the analytical method used to support the algae and daphnia studies is given in reference [21]. For evaluation of aquatic toxicity, the parent compound itself was tested since its potential environmental effects were expected to be greater than its human or environmental metabolites. For a discussion and comparison of expected environmental behavior and predicted aquatic toxicity of metabolites versus parent see section 7.1. As a result of this QSAR evaluation, any adverse environmental effects observed during testing with ropinirole are expected to represent a 'worst-case' scenario, in terms of potential environmental impact from ropinirole or its metabolites.

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The L(E)C_{50} arithmetic mean for three distinct aquatic species exposed to ropinirole was calculated to be 27 ± 15 mg/L (std. dev.; n=3) as the free base. A memorandum summarizing the study of the acute toxicity of ropinirole to *Daphnia magna* is given as reference [22] in Confidential Attachment 2. A detailed report on the acute toxicity of ropinirole to the green algae *Selenastrum capricornutum* is given as reference [14] in Confidential Attachment 2. The full report on the contract laboratory study of the acute toxicity of ropinirole to bluegill sunfish (*Lepomis macrochirus*) is given as reference [23] in Confidential Attachment 2. Microbics Microtox® tests conducted on ropinirole produced an EC_{50} of 413 ± 27 mg/L as the hydrochloride salt (SmithKline Beecham Laboratory Notebook #22262: pp.167-168). This is equivalent to 362 mg/L ropinirole as the free base.

The results of the studies described above are summarized below.

Toxicity Test	Ropinirole (mg free base/L)
Daphnia magna (48-hour exposure)	
LC_{50}	41.1[a]
NOEC	4.4[a]
Selenastrum capricornutum (14-day exposure)	
EC_{50} (biomass response)	29.3
NOEC (biomass and concentration)	8.8
Bluegill sunfish (*Lepomis macrochirus*) (96-hour exposure)	
LC_{50}	11.0
NOEC	3.7
Microbics Microtox® (15-minute EC_{50})	362

[a] preliminary data

8.3. Other Toxicity Studies

8.3.1. Acute Microbial Inhibition

A memo summarizing the study of the acute microbial inhibition of ropinirole is given as reference [24]. Ropinirole had no statistically significant (P=0.27) effect upon freshly-collected activated sludge oxygen utilization rates over 2.5 hours up to the highest concentration tested, 500 mg/L. Therefore, at expected environmental concentrations,

Amended page

ropinirole is not expected to have any adverse impact on typical activated sludge operations of a wastewater treatment plant.

8.4. Summary: Predicted Environmental Effects of Ropinirole in the Environment

At concentrations expected to be emitted into and exist in the environment (see Confidential Attachment 7), ropinirole and its metabolites should exhibit no toxic effects upon organisms in the environment. Thus, the production and use of ropinirole tablets are not expected to have any adverse impacts on the environment.

9. USE OF RESOURCES AND ENERGY

9.1. Use of Resources And Energy At Cork

The following table summarizes the percent of total plant resources expected to be utilized at the Cork facility to produce ropinirole drug substance during the 4th year of production. Details on expected resource use at Cork are presented in Confidential Table 20 in Confidential Attachment 6.

	Electricity (Kw-hour)	Natural Gas (Therms)	Water (Gallons)
Percent Consumption	1.15%	0.8%	0.8%

The effects on the use of resources and land for the production of ropinirole drug substance are minimal because of the relatively low production volumes and associated wastes, and the existing treatment units that will be used.

9.1.1. Effect Upon Endangered Species And Historic Places

The production of ropinirole substance and the disposal of associated wastes should have no impact on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by ropinirole substance production or waste disposal activities since the production will take place outside of the United States.

9.2. Use of Resources And Energy at Worthing

The average daily consumption of energy and resources at Worthing in 1994 is presented in Confidential Table 21 in Confidential Attachment 6. Since Worthing may produce ropinirole drug substance, at quantities that are scale-dependent, an accurate assessment of resource use cannot be determined. However, based on the expected overall production quantities of ropinirole for consumption in the US (see Confidential Attachment 6), a relatively small percentage of resources would be expected to be used for ropinirole production at the Worthing site.

9.2.1. Effect Upon Endangered Species And Historic Places

The production of ropinirole drug substance and the disposal of associated wastes by Worthing should have no effect on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by product production or waste disposal activities since the production of drug substance would take place outside of the United States.

9.3. Use of Resources and Energy at Crawley

The consumption of resources (electricity and water) expected at Crawley during the 5th year of production is presented in Confidential Table 22 in Confidential Attachment 6. Given the anticipated production volume of ropinirole tablets, and the known amounts of resources used by the Crawley facility (confidential), it is expected that only a small percentage of the total resources and energy used at the Crawley facility will be used for the ropinirole drug product.

9.3.1. Effect Upon Endangered Species And Historic Places

The production of ropinirole tablets and the disposal of associated wastes should have no effect on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by ropinirole tablet production or waste disposal activities since the production will take place outside of the United States.

10. MITIGATION MEASURES

10.1. Mitigation At Cork

Plans to minimize waste output have been considered and implemented at the outset of ropinirole development and production. The Integrated Pollution Control (IPC) license contains guidelines for the establishment of an Environment Management Programme to assess all operations for the use of cleaner technology and the minimization of waste. Potential environmental impacts associated with production at Cork are also minimized by the following:

Most waste streams are incinerated, and the gases scrubbed before being discharged. Scrubber liquors are biotreated in the on-site wastewater treatment facility before being discharged;

Several waste streams from ropinirole production will be sent off-site for recovery of solvents; and one waste stream will be sent off-site for recovery of a catalyst; and

Airstreams from the process buildings are scrubbed prior to venting to the atmosphere.

10.2. Mitigation At Worthing

Potential environmental impacts associated with drug substance production at Worthing are minimized by the following:

Airstreams from the process buildings are filtered prior to venting to the environment;

The Worthing facility is required to minimize gaseous emissions in accordance with their process authorizations as granted by HMIP, and all reactor outlets are scrubbed as necessary; and

All storage vessels are contained within spillage bunds (dikes), in accordance with Health and Safety Executive guidelines on the storage of flammable liquids and other materials.

10.2.1. Resource Recovery

During the ropinirole production processes at Worthing, several solvents and a catalyst would be recovered from some of the waste streams prior to their disposal to dilute aqueous waste or off-site disposal.

10.3. Mitigation At Crawley

Potential adverse environmental impacts associated with the proposed action are minimized at the Crawley facility by the following:

All reactions are carried out under closed systems wherever possible to minimize creating excessive dust, and local exhaust ventilation is used in areas of activity, such as loading and unloading materials; and

Dilute aqueous waste disposed of through the site aqueous effluent goes to a publicly owned treatment works; the effluent discharge has to meet certain waste treatment parameter criteria. See Item 6 for additional details.

11. ALTERNATIVE TO THE PROPOSED ACTION:

No potential adverse environmental impacts have been identified for the proposed action. The only alternative to the proposed action is that of no action, thus depriving patients an important therapy. The approval of ropinirole for the treatment of Parkinson's disease will provide an important benefit to patients requiring its administration with no known adverse environmental risk.

ENVIRONMENTAL ASSESSMENT

Ropinirole (SK&F 101468) Tablets

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12. LIST OF PREPARERS:

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(See Appendix VII for Curricula Vitae of contributors and preparers)

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13. CERTIFICATION:

- The undersigned official certifies that the information presented is true, accurate, and complete to the best knowledge of the Environmental Research Laboratory of SmithKline Beecham.

Date: 29.9.95

Signature: George Wellman

Dr. George Wellman
Vice President & Director
Chemical Development
SmithKline Beecham

14. REFERENCES:

1. Physicochemical Characterization of SK&F 101468-A, SmithKline and French Laboratories, SK&F Report CP002BA, August 1986.

2. SmithKline Beecham Pharmaceuticals; "A Study to Investigate the Pharmacokinetics and to Profile the Metabolites of ^{14}C Labelled SK&F 101468 when Administered by the Intravenous and Oral Route to Healthy Male Subjects", SB Report No. HF-1001/SK&F 101468/1/CPMS-011, 14 July 1992

3. ClogP version 3.64 log P estimation program, Pomona College Database, 28 June 1995

4. "Biodegradation Half-Life Analysis", QSAR (*Quantitative Structure/Activity Relationships*), Institute for Process Analysis, Montana State University, through Technical Database Services, Inc., 10 Columbus Circle, New York, NY 10019, from Neimi, G.J., Gilman, V.D., Regal, R.R., and Vaischnar, D.D., "Structure Features Associated with Biodegradation and Persistent Chemicals", Natural Resources Research Institute, University of Minnesota, Duluth, MN

5. Health Designs, Inc., Rochester, New York, USA. TOPKAT®

6. Further Physicochemical Properties of SK&F 101468-A; SmithKline and French Research, Ltd., SK&F Report CW002BA, July 1987.

7. P.S. Ziegenfuss, Report No. ERL9514, "SK&F 101468 (Ropinirole): Octanol/Water Distribution and Partition Coefficients", September 21, 1995

8. P.S. Ziegenfuss, Report No. ERL9510, "SK&F 101468 (Ropinirole): Henry's Law Constant", August 8, 1995

9. P.S. Ziegenfuss, Report No. ERL9512, "SK&F 101468 (Ropinirole): Adsorption to Activated Sludge," August 15, 1995

10. P.S. Ziegenfuss, Report No. ERL9506, "SK&F 101468 (Ropinirole): UV/VIS Spectra and Direct Aquatic Photolysis Kinetics," September 21, 1995

11. SmithKline Beecham ERL Memorandum, L. Hsu/B. Hannah, "SK&F 101468-A: Analytical Method for Ropinirole Fate Studies", Study # 95009, July 7, 1995

12. P.S. Ziegenfuss, Report No. ERL9511, "SK&F 101468 (Ropinirole): Cometabolic Mineralization in Activated Sludge," August 8, 1995

13. ERL Memorandum, D.R. Orvos/V. Cunningham, "Ropinirole HCL (SK&F 101468-A) - Assessment of Biodegradation", June 5, 1995

14. SmithKline Beecham ERL Memorandum, D.R. Orvos and L.C. Hsu, "SK&F 101468A (Ropinirole HCL): Acute Algal Toxicity", Study #94-004, Report # ERL9513, August 10, 1995

15. ERL Memorandum, L. Hsu/R. Hannah, D. Orvos, "Summary of CERL Study 95-008: Ropinirole Algal Metabolites", August 30, 1995

16. ERL Memorandum, J. Brum/B. Hannah, "Ropinirole Algal Transformation (Study #95-008 DRO): Analysis via LC/ESI/MS", August 23, 1995

17. Leifer, A. 1988, *The Kinetics of Environmental Aquatic Photochemistry: Theory and Practice*, American Chemical Society, Washington, D.C. 304 pps.

18. Vincent, P.G. "FDA NEPA Strategy Perspective", Invitational Paper Presentation, American Institute of Chemical Engineers, August 18-21, 1991, Pittsburgh, PA, p. 13-15

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20. Wildlife International Ltd., Project Number 374C-106, "Analytical Method Verification for the Determination of SK&F 101468-A (Ropinirole HCL) Residues in Freshwater", June 5, 1995

21. SmithKline Beecham Pharmaceuticals, HPLC Procedure and Validation for the Impurity Profile and Assay of SK&F 101468-A, Analytical Chemistry Report Number 81, 29 May 1991, 26 pp.

22. ERL Memorandum, Dr. D. Orvos/V. Cunningham, "Ropinirole HCL (SK&F 101468A) - Preliminary Acute *Daphnia* Toxicity Test", May 31, 1995

23. SK&F 101468-A (Ropinirole HCL): "A 96-Hour Static Acute Toxicity Test with the Bluegill Sunfish", Wildlife International Ltd., Project Number 374A-101, May 30, 1995

24. SmithKline Beecham ERL Memorandum, D. Orvos/V. Cunningham, "Ropinirole HCL (SK&F 101468A) - Acute Microbial Inhibition Test", May 31, 1995

25. U.S. EPA, "1984 Need Survey: Report to Congress: Assessment of Needed Publicly Owned Waste Water Treatment Facilities in the U.S.", EPA 430-9-84-011, U.S EPA, 1984

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APPENDICES:

15.1. Appendix I: Documentation for Disposal of Drug Product
- 15.1.1 SmithKline Beecham Pharmaceuticals, Bristol, Tennessee
- 15.1.2 Ogden Martin Systems of Lake, Inc.

15.2. Appendix II: Drug Substance Production at Cork
- 15.2.1 Certification of Compliance
- 15.2.2 Consent Limits

15.3. Appendix III: Drug Substance Production at Worthing
- 15.3.1 Certification of Compliance
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15.4 Appendix IV: Drug Product Production at Crawley
- 15.4.1 Certification of Compliance.
- 15.4.2 Consent Limits

15.5. Appendix V: Material Safety Data Sheet/Data Summary
- 15.5.1 MSDS for Ropinirole
- 15.5.2. Data Summary for Ropinirole

15.6 Appendix VI: Statutory Instruments for the United Kingdom (Worthing, Cork, Crawley)

15.7 Appendix VII: Curricula Vitae of Preparers
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- 15.7.2. Robert E. Hannah
- 15.7.3. David C. Constable, Ph.D.
- 15.7.4. Leo C. Hsu, Ph.D.
- 15.7.5. P. Scott Ziegenfuss
- 15.7.6. David R. Orvos, Ph.D.
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- 15.7.11.Ajit K. Ghorpade, Ph.D.
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- 15.7.15.Diane M. Yardley (Worthing, UK)
- 15.7.16.Dennis B. Hallifax (Crawley, UK)

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CONFIDENTIAL ATTACHMENTS

15.8 Confidential Attachment 1: Study Reports -

15.9 Confidential Attachment 2: Study Reports -

15.10 Confidential Attachment 3:
15.10.1.

15.11 Confidential Attachment 4:
15.11.1.

15.12 Confidential Attachment 5:
15.12.1.

15.13. Confidential Attachment 6:
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TENNESSEE AIR POLLUTION CONTROL BOARD
NASHVILLE, TENNESSEE 37247-3101

OPERATING PERMIT Issued Pursuant to Tennessee Air Quality Act

Date Issued: APR 2 ~ 1992
(or) November 1, 1995

Permit Number: 032714I

Date Expires:

Issued To:
Beecham Laboratories

Installation Address:
Bristol Industrial Park
Bristol

Installation Description:
Infectious Waste and
Pharmaceutical Incinerator
Consumat C-325PA-1.5R
Automatic Mechanical Loader

Emission Source Reference No:
82-0191-13

The holder of this permit shall comply with the conditions contained in this permit as well as all applicable provisions of the Tennessee Air Pollution Control Regulations.

CONDITIONS:

1. This permit does not cover any air contaminant source that does not conform to the conditions of this permit and the information given in the approved application. This includes compliance with the following operating parameters:

   Charging rate shall not exceed 860 lb/hr.

2. Hydrogen chloride (HCl) emitted from this source shall not exceed 4.515 lb/hr.

3. Particulate matter emitted from this source shall not exceed 0.1 grains per dry standard cubic foot of exhaust gas corrected to 12% carbon dioxide.

4. Natural gas only shall be used as fuel(s) for this source.

5. This incinerator shall be operated with a minimum secondary chamber temperature of 1600°F.

(continued on the next page)

TECHNICAL SECRETARY FS071284

No Authority is Granted by this Permit to Operate, Construct, or Maintain any Installation in Violation of any Law, Statute, Code, Ordinance, Rule or Regulation of the State of Tennessee or any of its Political Subdivisions.

NON TRANSFERABLE POST OR FILE AT INSTALLATION ADDRESS

PH-2561
APC Rev. 1/92

APR 2 9 1992

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6. The secondary chamber temperature shall be continuously monitored and recorded. Sensors shall be installed, maintained, and operated such that the flames from the burners do not impinge upon the sensors. The secondary chamber temperature shall be measured at or beyond the chamber exit. The temperature sensing device shall have an accuracy that is plus or minus 25°F over its operating range. The recorders must have a minimum chart speed of one (1) inch per hour for strip chart recorders and a maximum of 24 hours per chart for circular recorders.

7. Visible emissions from this infectious waste incinerator must meet an emission limit of ten (10) percent opacity, except for one six (6) minute period per hour of not more than twenty (20) percent opacity, as specified in Rule 1200-3-25-.05(3). The opacity is to be measured by EPA Method 9, as published in the Federal Register, Volume 39, No. 219, November 12, 1974. This opacity standard shall not apply to burner startups when only firing auxiliary fuel without waste being burned.

8. Sixty (60) days prior to the expiration of this permit, permittee shall apply for permit renewal.

9. This source shall comply with all the performance, emission specifications, and recordkeeping requirements of Rule 1200-3-25 of the Tennessee Air Pollution Control Regulations.

10. This incinerator must be equipped with an automatic mechanical loader.

11. This incinerator may not be charged more than 4 times per hour.

12. The approved operating procedures shall be posted on-site at or near the incinerator and followed at all times.

13. Inspection and maintenance schedules shall be posted or kept on-site at or near the incinerator.

14. Records shall be kept of inspections, maintenance, and repairs.

15. Records shall be maintained at the source for a minimum of two years form the date compiled and shall be made available for review upon request of the Technical Secretary or his agent.

(continued on the next page)

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16. A log of the following information must be maintained at the source location and kept available for inspection by the Technical Secretary or his representative:

    1. Weight of each charge
    2. Time of each charge
    3. Number of sharps containers per day

    This log must be retained for a period of not less than two years.

17. This source shall not burn anti-neoplastic agents.

18. A daily record shall be maintained of all product categories charged to the incinerator such as tablets, capsules, liquids, topicals, ampules, syringes, oral suspensions, and suppositories. The total quantity of halide in each product must be determined. Using this information, the quantity of halides incinerated daily must be recorded and calculation methods must be documented. These records must be maintained for two years.

19. The incinerator shall be charged with wastes that have a halide concentration as represented by the data supplied in the November 2, 1989, report to this Division including corrections, contained in the November 4, 1989, letter to this Division, and the data included with the correspondence dated October 25, 1991.

20. Any changes to the operating procedures for this source must be submitted to the Technical Secretary for approval.

FS071284

SERVICE AGREEMENT

This Agreement, by and between SmithKline Beecham Pharmaceuticals, 1704 Mid Park Drive, Knoxville, TN 37921, a Tennessee corporation, hereinafter referred to as "Customer," and Environmental Healthcare Incorporated, P.O. Box 2286, Delray Beach, FL, 33447, a Florida corporation, hereinafter referred to as "EHI" shall provide a service of nonhazardous waste transportation and incineration for the Customer on the following terms and conditions:

- This Agreement shall become effective as of the date of this Agreement and shall continue in effect unless and until either EHI or Customer gives the other party notice of termination of this Agreement.
- Ogden Martin Systems of Lake, Inc., hereinafter referred to as "designated disposal facility" will incinerate the materials in compliance with the State of Florida regulations governing municipal solid waste and biohazardous waste.
- Price Schedule- Schedule A.
- Packaging and loading will be accomplished by Customer in compliance with all local, state, and federal laws and regulations. Only non-regulated waste that has been approved by the designated disposal facility will be accepted. (See Appendix A) Appendix A may be amended from time to time in response to changes in Customer's product line.
- Material must be packaged and shipped in combustible containers. Bulk liquids must be shipped in either consumer packaging or containers not exceeding five gallons each. Bulk powders must be delivered in packaging with the total volume of powders not to exceed twenty gallons.
- By signing in the space provided below, the Customer acknowledges having read and that it is bound by the terms and conditions above and continuing on the reverse side of this page.
- This agreement is valid up to sixty (60) days from this offer.

Environmental Healthcare Incorporated	SmithKline Beecham Pharmaceuticals
Name: Brian Blum	Name: George M. McCormack
Title: President	Title: Manager, Distribution
Date: May 4, 1994	Date: May 16, 1994

SBPKNT050494

Environmental Healthcare Incorporated ™

Terms and Conditions

Wastes to be Transported and Disposed. Prior to arranging for the transportation and disposal of waste material, each waste stream must be approved by the designated disposal facility. EHI shall arrange for the transportation and disposal of such quantities of Wastes as Customer shall require from time to time during the term of this agreement. The list of approved wastes may be modified by the parties' agreement to an amendment. EHI reserves the right to decline to transport and dispose any waste which in EHI's judgment cannot be arranged in a lawful manner or without a risk of harm to public health or the environment.

Transportation. EHI shall be responsible for providing mutually acceptable means to transport the waste and Customer shall be responsible for loading the wastes. Transportation of materials must be scheduled with the EHI Representative. EHI shall provide a shipping manifest and Customer shall complete and present the manifest to the transporter with each shipment of waste in accordance with all applicable requirements of the United States Department of Transportation and all other statutes and regulations. The party that provides transportation shall comply with all DOT regulations. If wastes are spilled on equipment during loading operations, the party responsible for the loading shall thoroughly clean the equipment. The transporting party shall require all carriers it engages to carry vehicular insurance and shall, upon request, provide the other party with certificates of insurance proving such coverages. Customer shall provide satisfactory roadways and approaches to the point of loading. Unless otherwise agreed wastes will be loaded at Customer's place of business during normal business hours, Monday through Friday.

Samples. EHI may test samples drawn from the waste generated by the customer to determine whether it constitutes Unacceptable or Hazardous Waste. The cost of any such tests shall be borne by the customer if the results indicate that such waste contains Unacceptable or Hazardous Waste.

Warranties. Customer warrants that all Wastes which may be transported to the designated disposal facility pursuant to this agreement shall materially conform to the description of the approved Wastes. The designated disposal facility shall have a reasonable time after receipt of the Wastes to determine if they conform to the approved list. If the designated disposal facility deems that the Wastes do not conform to the approved list it will immediately advise EHI. EHI in turn will immediately advise Customer. If the designated disposal facility elects to reject the Wastes, they will prepare the Wastes for lawful transportation and return to the Customer, unless the designated disposal facility, EHI and Customer agree to some other disposition. The designated disposal facility shall be entitled to reimbursement from the Customer for the designated disposal facility's reasonable costs for handling, loading, preparing, transporting, storing and caring for rejected wastes. EHI warrants that its services, including transportation performed under this agreement shall comply with all requirements of federal, state and local laws, regulations and ordinances.

Indemnification. EHI agrees to indemnify, save harmless and defend Customer from and against any and all losses, damages or claims (including attorney's fees) relating to the loss of or damage to the property of or injury to or death of any person(s), resulting from or arising in any manner out of EHI's breach, willful misconduct, negligent act or omission of EHI, or from any violation by EHI of any municipal, state or federal laws, rules or regulations applicable to the performance of its obligations under this Agreement. Indemnification under this provision shall survive termination of the Agreement. Customer agrees to indemnify, save harmless and defend EHI from and against any and all losses, damages or claims (including attorney's fees) relating to the loss of or damage to the property of or injury to or death of any person(s), resulting from or arising in any manner out of Customer's breach of this agreement.

Charges and Fees. EHI will arrange the transportation and/or disposal at the rate set forth above. EHI reserves the right to adjust the rates quoted above to cover pro rata increases in fuel, insurance, disposal costs and increases in costs resulting from changes in regulatory requirements or guidelines. Customer will receive thirty (30) days notice prior to the effective date of any such adjustment. The designated disposal facility shall maintain and utilize motor truck scales of an accuracy consistent to state law to weigh all authorized delivery trucks. Each incoming truck will be initially weighed to determine it's gross weight and such weight will be recorded. Each outgoing truck will be subsequently weighed, and the tare weight will be recorded. Copies of weight tickets will be kept for a minimum of one year, and can be examined by Customer upon reasonable request during normal business hours.

Payment. Each invoice for Wastes transported and disposed shall be paid, net terms, by Customer within thirty (30) days from the disposal of waste. Customer shall pay interest on overdue payments at a rate of 1.5% per month. EHI may suspend service if payment is late. Suspension of service due to non-payment shall not constitute termination of this agreement.

Term. This agreement shall commence on the date written above and shall continue in full force until either party gives sixty (60) days written notice. Either party shall have the right to cancel this agreement at any time if the other party becomes insolvent, makes an assignment for the benefit of creditors, or has a bankruptcy petition filed by or against it.

Certification of Disposal. EHI will provide Customer with a certification of disposal verifying that designated Wastes have been properly disposed. This certification is part of the EHI Manifest, this Manifest must accompany all shipments.

General Provisions. In performance of this agreement EHI is an independent contractor. Each party agrees to protect and hold confidential any technologies observed while on the other's premises. EHI agrees to protect and hold confidential all data on Wastes received from the Customer.

Defaults. If during the term of this agreement, either party shall become delinquent in settling its account or shall be in default with any term of this agreement, the other party may suspend its performance hereunder until such delinquency or default has been corrected. Any delay or failure of either party in the performance of its required obligations hereunder shall be excused if and to the extent caused by acts of God, strikes, action of regulatory agencies, facility shutdown, loss of permit and cause or causes beyond the reasonable control of the party affected provided that a prompt notice of such delay is given by such party to the other and each of the parties hereto shall be diligent in attempting to remove such cause or causes.

Notice. Any notice required to be given by the terms of this agreement shall be mailed to EHI at the address as stated on opposite page; to the Customer at the address as stated on opposite page; or to such other address for either party as that party may designate.

Florida Department of Environmental Regulation

Central District • 3319 Maguire Boulevard, Suite 232 • Orlando, Florida 32803-3767

Lawton Chiles, Governor — Carol M. Browner, Secretary

Permittee:
Ogden Martin Systems of Lake, Inc.
40 Lane Road
Fairfield, NJ 07007-2615

Attention: Gary K. Crane, Ph.D.,
Exec. V.P.

I. D. Number:
Permit/Certification
Number: A035-193817
Date of Issue:
Expiration Date: October 25, 1996
County: Lake
Latitude/Longitude:
28°44'22"N/81°53'23"W
UTM: 17-413.12 KmE; 3179.21 KmN
Project: Waste to Energy Facility
Units No. 1 and 2

This permit is issued under the provisions of Chapter(s) 403, Florida Statutes, and Florida Administrative Code Rule(s) 17-2. The above named permittee is hereby authorized to perform the work or operate the facility shown on the application and approved drawing(s), plans, and other documents attached hereto or on file with the department and made a part hereof and specifically described as follows:

The permittee can operate two 250 ton-per-day Combustors which are fueled by wood chips and municipal solid waste.

The facility is rated for a maximum of 15.7 megawatts of energy production.

These sources are located at 3830 Rogers Industrial Park Road in Okahumpka, Lake County, Florida.

General Conditions are attached to be distributed to the permittee only.

Recycled Paper

GENERAL CONDITIONS:

1. *The terms, conditions, requirements, limitations and restrictions set forth in this permit, are "permit conditions" and are binding and enforceable pursuant to Sections 403.141, 403.727, or 403.859 through 403.861, F.S. The permittee is placed on notice that the Department will review this permit periodically and may initiate enforcement action for any violation of these conditions.*

2. *This permit is valid only for the specific processes and operations applied for and indicated in the approved drawings or exhibits. Any unauthorized deviation from the approved drawings, exhibits, specifications, or conditions of this permit may constitute grounds for revocation and enforcement action by the Department.*

3. *As provided in subsections 403.087(6) and 403.722(5), F.S., the issuance of this permit does not convey any vested rights or any exclusive privileges. Neither does it authorize any injury to public or private property or any invasion of personal rights, nor any infringement of federal, state, or local laws or regulations. This permit is not a waiver of or approval of any other Department permit that may be required for other aspects of the total project which are not addressed in this permit.*

4. *This permit conveys no title to land or water, does not constitute State recognition or acknowledgement of title, and does not constitute authority for the use of submerged lands unless herein provided and the necessary title or leasehold interests have been obtained from the State. Only the Trustees of the Internal Improvement Trust Fund may express State opinion as to title.*

5. *This permit does not relieve the permittee from liability for harm or injury to human health or welfare, animal, or plant life, or property caused by the construction or operation of this permitted source, or from penalties therefore; nor does it allow the permittee to cause pollution in contravention of Florida Statutes and Department rules, unless specifically authorized by an order from the Department.*

6. *The permittee shall properly operate and maintain the facility and systems of treatment and control (and related appurtenances) that are installed and used by the permittee to achieve compliance with the conditions of this permit, as required by Department rules. This provision includes the operation of backup or auxiliary facilities or similar systems when necessary to achieve compliance with the conditions of the permit and when required by Department rules.*

7. *The permittee, by accepting this permit, specifically agrees to allow authorized Department personnel, upon presentation of credentials or other documents as may be required by law and at reasonable times, access to the premises where the permitted activity is located or conducted to:*

   (a) *Have access to and copy any records that must be kept under conditions of the permit;*

   (b) *Inspect the facility, equipment, practices, or operations regulated or required under this permit; and*

   (c) *Sample or monitor any substances or parameters at any location reasonably necessary to assure compliance with this permit or Department rules.*

   Reasonable time may depend on the nature of the concern being investigated.

8. *If, for any reason, the permittee does not comply with or will be unable to comply with any condition or limitation specified in this permit, the permittee shall immediately provide the Department with the following information:*

   (a) *A description of and cause of noncompliance; and*

   (b) *The period of noncompliance, including dates and times; or, if not corrected, the anticipated time the noncompliance is expected to continue, and steps being taken to reduce, eliminate, and prevent recurrence of the noncompliance.*

The permittee shall be responsible for any and all damages which may result and may be subject to enforcement action by the Department for penalties or for revocation of this permit.

GENERAL CONDITIONS:

9. *In accepting this permit, the permittee understands and agrees that all records, notes, monitoring data and other information relating to the construction or operation of this permitted source which are submitted to the Department may be used by the Department as evidence in any enforcement case involving the permitted source arising under the Florida Statutes or Department rules, except where such use is prescribed by Section 403.111 and 403.73, F.S. Such evidence shall only be used to the extent it is consistent with the Florida Rules of Civil Procedure and appropriate evidentiary rules.*

10. *The permittee agrees to comply with changes in Department rules and Florida Statutes after a reasonable time for compliance; provided, however, the permittee does not waive any other rights granted by Florida Statutes or Department rules.*

11. *This permit is transferable only upon Department approval in accordance with Rule 17-4.120 and 17-30.300, F.A.C., as applicable. The permittee shall be liable for any non-compliance of the permitted activity until the transfer is approved by the Department.*

12. *This permit or a copy thereof shall be kept at the work site of the permitted activity.*

13. *This permit also constitutes:*

    (X) *Determination of Best Available Control Technology (BACT)*

    (X) *Determination of Prevention of Significant Deterioration (PSD)*

    ( ) *Certification of compliance with state Water Quality Standards (Section 401, PL 92-500)*

    (X) *Compliance with New Source Performance Standards*

14. *The permittee shall comply with the following:*

    (a) *Upon request, the permittee shall furnish all records and plans required under Department rules. During enforcement actions, the retention period for all records will be extended automatically unless otherwise stipulated by the Department.*

    (b) *The permittee shall hold at the facility or other location designated by this permit records of all monitoring information (including all calibration and maintenance records and all original strip chart recordings for continuous monitoring instrumentation) required by the permit, copies of all reports required by this permit, and records of all data used to complete the application for this permit. These materials shall be retained at least three years from the date of the sample, measurement, report, or application unless otherwise specified by Department rule.*

    (c) *Records of monitoring information shall include:*

        1. *the date, exact place, and time of sampling or measurements;*
        2. *the person responsible for performing the sampling or measurements;*
        3. *the dates analyses were performed;*
        4. *the person responsible for performing the analyses;*
        5. *the analytical techniques or methods used;*
        6. *the results of such analyses.*

15. *When requested by the Department, the permittee shall within a reasonable time furnish any information required by law which is needed to determine compliance with the permit. If the permittee becomes aware the relevant facts were not submitted or were incorrect in the permit application or in any report to the Department, such facts or information shall be corrected promptly.*

PERMITTEE:
Ogden Martin Systems of Lake, Inc.

Attention: Gary K. Crane, Ph.D.,
Exec. V.P.

I. D. Number:
Permit/Certification Number:
A035-193817
Date of Issue:
Expiration Date: October 25, 1996

SPECIFIC CONDITIONS:

OPERATING CONDITIONS

1. Municipal Waste Combustor

   a. Each of the two municipal waste combustors (MWC) shall have a design rated capacity of 250 tons of Municipal Solid Waste (MSW) per day, 104 million Btu input per hour and 60,200 pounds steam output per hour with MSW having a heating value of 5,000 Btu per pound.

   b. The maximum individual MWC throughput shall not exceed 250 tons per day, 120 million Btu per hour and 69,000 pounds steam per hour, (3-hour average).

   c. The design furnace mean temperature at the fully mixed zone of the combustor shall be no less than 1800° for a combustion gas residence time of at least one second.

   d. The MWC shall be fueled with wood chips or municipal solid waste. Radioactive waste may not be burned unless the combustor has been issued a permit for such burning or the waste is such quantity to be exempt in accordance with Department of Health and Rehabilitative Services (HRS) Rule 10D-91 or 10D-104.003, F.A.C. Hazardous waste may not be burned unless the combustor has been issued a permit for such burning or the waste is of such quantity to be exempt in accordance with Department Rule 17-30, F.A.C. Other wastes and special wastes shall not be burned without specific prior written approval of the Florida DER.

   e. Auxiliary fuel burners shall be fueled only with distillate fuel oil or gas (e.g., natural or propane). The annual capacity factor for fuel oil or gas shall be less than 10%, as determined by 40 CFR 60.43b(d). If the annual capacity factor for fuel oil or gas is greater than 10%, the facility shall be subject to 40 CFR 60.44b, standards for nitrogen oxides.

   f. Auxiliary fuel burner(s) shall be used at start up during the introduction of MSW fuel until design furnace gas temperature is achieved. All air pollution control and continuous emission monitoring equipment shall be operational and functioning properly prior to the incineration or ignition of waste and until all the wastes are incinerated. During shut down, the combustion chamber temperature requirement shall be maintained using auxiliary burners until wastes are complete combusted.

g. The facility may operate continuously (8760 hrs/yr).

h. The combustor shall be fed so as to prevent opening the combustor to the room environment.

2. Air Pollution Control Equipment Design

a. Each MWC shall be equipped with a particulate emission control device.

b. Each MWC shall be equipped with an acid gas control device designed to remove at least 90% of acid gases and 70% sulfur dioxide emissions.

c. The acid gas emission control system shall be designed to be capable of cooling flue gases to an average temperature not exceeding 300°F (3-hour rolling average).

3. Continuous Emission Monitoring

Continuous emission monitors for opacity, oxygen, carbon monoxide, carbon dioxide, and sulfur dioxide shall be installed, calibrated, maintained and operated for each unit.

a. Each continuous emission monitoring system (CEMS) shall meet performance specifications of 40 CFR 60, Appendix B. The SO_2 CEMS sample point shall be located downstream of control devices for each unit.

b. CEMS data shall be recorded during periods of startup, shutdown and malfunction but shall be excluded from emission averaging calculations for CO, SO_2, and opacity.

c. A malfunction means any sudden and unavoidable failure of air pollution control equipment or process equipment to operate in a normal or usual manner. Failures that are caused entirely or in part by poor maintenance, careless operation or any other preventable upset condition or preventable equipment breakdown shall not be considered malfunctions.

d. The procedures under 40 CFR 60.13 shall be followed for installation, evaluation and operation of all CEMS.

e. Opacity monitoring system data shall be reduced to 6-minute averages, based on 36 or more data points, and gaseous CEMS data shall be reduced to 1-hour averages, based on 4 or more data points, in accordance with 40 CFR 60.13(h).

f. Average CO and SO_2 emission concentrations corrected for CO_2, shall be computed in accordance with the appropriate averaging time periods included in Condition No. 3.

g. For purposes of reports required under this permit, excess emissions are defined as any calculated average emission concentration, as determined pursuant to Condition No. 3 herein, which exceeds the applicable emission limit in Condition No. 7.

4. Operations Monitoring

a. Devices are to be used to continuously monitor and record steam production, furnace exit gas temperature (FEGT) and flue gas temperature at the exit of the acid gas control equipment. An FEGT to combustion zone correlation shall be established to relate furnace temperature at the temperature monitor location to furnace temperature in the overfire air fully mixed zone. This correlation shall be continuously available for inspection at the site.

b. The furnace heat load shall be maintained between 80% and 100% of the design rated capacity during normal operations. The lower limit may be extended provided compliance with the carbon monoxide emissions limit and the FEGT within this permit at the extended turndown rate are achieved.

5. Any change in the method of operation, fuels, equipment or operating hours shall be submitted for prior approval to DER's Central District office.

6. In order for the burning of biohazardous waste to be incorporated into the operation permit, the Department must receive reasonable assurance including but not limited to:

a. Particulate matter emissions shall not exceed 0.020 grains per dry standard cubic foot of flue gas, corrected to 7% O_2. (See Table 700-1)

b. Hydrochloric acid (HCL) emissions shall not exceed 50 parts per million by volume, dry basis, corrected to 7% O_2 on a three hour average basis or shall be reduced by 90% by weight on an hourly average basis. (See Table 700-1)

PERMITTEE:
Ogden Martin Systems of Lake, Inc.

Attention: Gary K. Crane, Ph.D.,
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c. This facility is subject to the following design, operating, monitoring and operator training requirements.

1. The source shall be designed to provide for a residence time of at least of at least one second in the secondary (or last) combustion chamber only, at no less than 1800°F for the combustion gases. Primary chamber and stack shall not be utilized in calculating this residence time.

2. Mechanically fed facilities shall incorporate an air lock system to prevent opening the source to the room environment. The volume of the loading system shall be designed to prevent overcharging thereby assuring complete combustion of the waste.

3. Carbon monoxide (CO) emissions shall not exceed 100 parts per million by volume, dry basis, corrected to 7% O_2 on an hourly basis. (See Table 700-1)

4. Incineration or ignition of waste shall not begin until the secondary (or last) combustion chamber temperature requirement is attained. All control equipment shall be operational and functioning properly prior to the incineration or ignition of waste and until all the wastes are incinerated. During shutdown, the secondary (or last) combustion chamber temperature requirement shall be maintained using auxiliary burners until the wastes are completely combusted.

5. Radioactive waste may not be burned unless the source has been issued a permit or the waste is of such quantity to be exempt in accordance with Rule 10D-91 or 10D104.003, F.A.C.

6. Hazardous waste may not be burned unless the source has been issued a permit or the waste is of such quantity to be exempt in accordance with Rule 17-30, F.A.C.

7. All biological waste combustor operators shall be trained by the equipment manufacturer's representatives or another qualified organization as to proper operating practices and procedures. The content of the training program shall be submitted to the Department for approval. The applicant shall submit a copy of a certificate verifying the satisfactory completion of a department approved training program prior to issuance or renewal of the operating permit. The applicant shall not operate the source unless it is operated by an operator who has satisfactorily completed the required training program.

d. Each owner or operator of biological waste incineration facility shall install, operate, and maintain in accordance with the manufacturer's instructions continuous emission monitoring equipment.

(1) The monitors shall record secondary (or last) combustion chamber exit temperature and oxygen.

(2) Any owner or operator subject to the provisions of Rule 17-2.710(5), F.A.C. shall maintain a complete file of all measurements, including continuous emissions monitoring system, monitoring device, and performance testing measurements; all continuous emissions monitoring system or monitoring device, calibration checks; adjustments and maintenance performed on these systems or devices; and all other information required, recorded in a permanent legible form suitable for inspection. The file shall be retained for at least two years following the date of such measurements, maintenance, reports and records.

e. Biohazardous waste may be incinerated by the applicant for the purpose of stack testing to demonstrate reasonable assurance and compliance with the regulations, and for a period not to exceed 90 days for report submittal and Department review. The compliance test must provide the Department with reasonable assurance that the biohazardous standards are met and must be conducted no later than 5 days after the incineration of biohazardous waste begins. The test must be conducted while combusting the maximum desired rate of biohazardous waste and this rate must be determined during the test.

EMISSION LIMITS

7. Flue gas emissions from each unit shall not exceed the following:

a. Particulate:	0.0150 grains/dscf corrected to 12% CO_2, or 0.020 grains/dscf corrected to 7% O_2, whichever is less
b. Sulfur Dioxide:	60 ppmdv corrected to 12% CO_2, 6-hour rolling average; or, 70% reduction of uncontrolled SO_2 emissions, 6-hour rolling average. Not to exceed 120 ppmdv corrected to 12% CO_2, 6-hr rolling average.

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c. Nitrogen Oxides:	385 ppmdv corrected to 12% CO_2.
d. Carbon Monoxide:	100 ppmdv corrected to 7% O_2 on an hourly-average basis.
e. Volatile Organic Compounds:	70 ppmdv as carbon corrected to 12% CO_2.
f. Lead:	3.1×10^{-4} gr/dscf corrected to 12% CO_2.
g. Fluoride:	1.5×10^{-3} gr/dscf corrected to 12% CO_2.
h. Beryllium:	2.0×10^{-7} gr/dscf corrected to 12% CO_2.
i. Mercury:	3.4×10^{-4} gr/dscf corrected to 12% CO_2.
j. Visible emissions:	Opacity of MWC emissions shall not exceed 15% opacity (6-min. average), except for one 6-min. period per hour of not more than 20% opacity. Excess emissions resulting from startup, shut down, or malfunction shall be permitted provided that best operational practices to minimize emissions are adhered to, and the duration of excess emissions are minimized.
k. Hydrochloric Acid:	50 ppmdv, corrected to 7% O_2 on a three hour average basis; or shall be reduced by 90% by weight on an hourly average basis.

For each pollutant for which a continuous emissions monitoring system is required in Condition No. 3, the emission averaging time specified above shall be used to establish operating limits and reportable excess emissions.

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Compliance with the permit emission limits shall be determined by EPA reference methods tests included in 40 CFR Parts 60 and 61 and listed in Conditions No. 8 of this permit or by equivalent methods approved by Florida DER.

COMPLIANCE

8. Compliance tests

a. Annual compliance tests shall be conducted at yearly intervals from the date of January 15, 1991 for particulate matter, nitrogen oxides, carbon monoxide, and HCL.

b. Annual compliance tests for the opacity standard shall be conducted at yearly intervals from the date of January 15, 1991 in accordance with 40 CFR 60.11(b) and (e).

c. At least 90 days prior to permit expiration date, the applicant must demonstrate compliance with each permitted emission limit in Specific Condition #7.

d. Compliance with the requirement for 70% control of sulfur dioxide emissions will be determined by using the test methods listed below or a continuous emission monitoring system for SO_2 emissions before and after the air pollution control equipment which meet the requirements of Performance Specification 2 of 40 CFR 60, Appendix B.

e. The compliance tests shall be conducted at the maximum capacity and at the maximum firing rate.

f. The following test methods and procedures of 40 CFR Parts 60 and 61 or equivalent methods shall be used for compliance testing:

(1) Method 1 for selection of sample site and sample traverses.

(2) Method 2 for determining stack gas flow rate.

(3) Method 3 or 3A for gas analysis for calculation of percent O_2 and CO_2.

(4) Method 4 for determining stack gas moisture content to convert the flow rate from actual standard cubic feet to dry standard cubic feet.

(5) Method 5 or Method 17 for concentration of particulate matter.

(6) Method 9 for visible determination of the opacity of emissions as required in this permit in accordance with 40 CFR 60.11.

(7) Method 6, 6C, or 8 for concentration of SO_2.

(8) Method 7, 7A, 7B, 7C, 7D, or 7E for concentration of nitrogen oxides.

(9) Method 10 for determination of CO concentration.

(10) Method 12 for determination of lead concentration.

(11) Method 13B for determination of fluoride concentration.

(12) Method 25 or 25A for determination of VOC concentration.

(13) Method 101A for determination of mercury emission rate.

(14) Method 104 for determination of beryllium emission rate.

(15) Method 26 for determination of hydrogen chloride emission rate.

REPORTS

9. Reporting

a. Fifteen (15) days prior notification in writing of compliance tests shall be given to the Florida DER district office.

b. The results of compliance test shall be submitted to the Central District office within 45 days after completion of the test.

c. The owner or operator shall submit excess emission reports for any calendar quarter during which there are excess emissions from the facility. If there are no excess emissions during the calendar quarter, the owner or operator shall submit a report semiannually stating that no excess emissions occurred during the semiannual reporting period. The report shall include the following:

(1) The magnitude of excess emissions computed in accordance with 40 CFR 60 CFR 60.13(h), any conversion factors used, and the date and time of commencement and completion of each period of excess emissions (60.7(c)(1)).

(2) Specific identification of each period of excess emissions that occurs during startups, shutdowns, and malfunctions of the furnace boiler system. The nature and cause of any malfunction (if known) and the corrective action taken or preventive measured adopted (60.7(c)(2)).

(3) The date and time identifying each period during which the continuous monitoring system was inoperative except for zero and span checks, and the nature of the system repairs or adjustments (60.7(c)(3)).

(4) When no excess emissions have occurred or the continuous monitoring system has not been inoperative, repaired, or adjusted, such information shall be stated in the report (60.7(c)(4)).

(5) The owner or operator shall maintain a file of all measurements, including continuous monitoring systems performance evaluations; monitoring systems or monitoring device calibration; checks; adjustments and maintenance performed on these systems or devices; and all other information required by this permit recorded in a permanent form suitable for inspection (60.7(d)).

d. Each calendar year on or before March 1, submit for each source, an Annual Operations Report DER Form 17-1.202(6) for the preceding calendar year.

PERMITTEE:
Ogden Martin Systems of Lake, Inc.

Attention: Gary K. Crane, Ph.D.,
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Expiration Date: October 25, 1996

SPECIFIC CONDITIONS:
(Continued)

...

(5) The owner or operator shall maintain a file of all measurements, including continuous monitoring systems performance evaluations; monitoring systems or monitoring device calibration; checks; adjustments and maintenance performed on these systems or devices; and all other information required by this permit recorded in a permanent form suitable for inspection (60.7(d)).

d. Each calendar year on or before March 1, submit for each source, an Annual Operations Report DER Form 17-1.202(6) for the preceding calendar year.

EXPIRATION DATE

10. An operation permit renewal must be submitted at least 60 days prior to the expiration date of this permit (Rule 17-4.09, F.A.C.).

ISSUED 12-6-91

STATE OF FLORIDA DEPARTMENT
OF ENVIRONMENTAL REGULATION

By [signature]
A. Alexander, District Director
3319 Maguire Boulevard, Suite 232
Orlando, Florida 32803

Florida Department of Environmental Regulation

Central District • 3319 Maguire Boulevard, Suite 232 • Orlando, Florida 32803-3767 • 407-894-7555

Bob Martinez, Governor Dale Twachtmann, Secretary John Shearer, Assistant Secretary
Alex Alexander, Deputy Assistant Secretary

Permittee:
Ogden Martin Systems of Lake, Inc.
40 Lane Road
Fairfield, New Jersey 07007-2615

Attention: Dr. Gary Crane
Executive Vice President

I. D. Number:
Permit/Certification Number
S035-187342
Date of Issue:
Expiration Date: 12/20/95
County: Lake
Section/Township/Range:
15 & 22/20 South/24 East
Latitude/Longitude:
28°44'25"/81°53'20"
Project: Lake County Resource Recovery Facility

This permit is issued under the provisions of Chapter(s) 403, Florida Statutes, and Florida Administrative Code Rule(s) 17-4 and 17-701. The above named permittee is hereby authorized to perform the work or operate the facility shown on the application and approved drawing(s), plans, and other documents attached hereto or on file with the department and made a part hereof and specifically described as follows:

To operate the Lake County Resource Recovery Facility designed to receive, handle and combust solid waste for the generation of steam and power.

The facility occupies 13.5 acres and is within the property boundary of 15.0 acres.

The facility has a maximum processing rate of 528 tons/day nominal which includes operating 24 hours per day, seven (7) days per week.

LOCATION: The waste to energy facility is located west of Haywood Farm Road, one-half mile south of County Road 48 on 3830 Rogers Industrial Park Road in Okahumpka, in Lake County, Florida.

General Conditions are attached to be distributed to the permittee only.

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GENERAL CONDITIONS:

1. The terms, conditions, requirements, limitations and restrictions set forth in this permit, are "permit conditions" and are binding and enforceable pursuant to Sections 403.141, 403.727, or 403.859 through 403.861, F.S. The permittee is placed on notice that the Department will review this permit periodically and may initiate enforcement action for any violation of these conditions.

2. This permit is valid only for the specific processes and operations applied for and indicated in the approved drawings or exhibits. Any unauthorized deviation from the approved drawings, exhibits, specifications, or conditions of this permit may constitute grounds for revocation and enforcement action by the Department.

3. As provided in subsections 403.087(6) and 403.722(5), F.S., the issuance of this permit does not convey any vested rights or any exclusive privileges. Neither does it authorize any injury to public or private property or any invasion of personal rights, nor any infringement of federal, state, or local laws or regulations. This permit is not a waiver of or approval of any other Department permit that may be required for other aspects of the total project which are not addressed in this permit.

4. This permit conveys no title to land or water, does not constitute State recognition or acknowledgement of title, and does not constitute authority for the use of submerged lands unless herein provided and the necessary title or leasehold interests have been obtained from the State. Only the Trustees of the Internal Improvement Trust Fund may express State opinion as to title.

5. This permit does not relieve the permittee from liability for harm or injury to human health or welfare, animal, or plant life, or property caused by the construction or operation of this permitted source, or from penalties therefore; nor does it allow the permittee to cause pollution in contravention of Florida Statutes and Department rules, unless specifically authorized by an order from the Department.

The permittee shall properly operate and maintain the facility and systems of treatment and control (and related appurtenances) that are installed and used by the permittee to achieve compliance with the conditions of this permit, as required by Department rules. This provision includes the operation of backup or auxiliary facilities or similar systems when necessary to achieve compliance with the conditions of the permit and when required by Department rules.

7. The permittee, by accepting this permit, specifically agrees to allow authorized Department personnel, upon presentation of credentials or other documents as may be required by law and at reasonable times, access to the premises where the permitted activity is located or conducted to:

   (a) Have access to and copy any records that must be kept under conditions of the permit;

   (b) Inspect the facility, equipment, practices, or operations regulated or required under this permit; and

   (c) Sample or monitor any substances or parameters at any location reasonably necessary to assure compliance with this permit or Department rules.

Reasonable time may depend on the nature of the concern being investigated.

8. If, for any reason, the permittee does not comply with or will be unable to comply with any condition or limitation specified in this permit, the permittee shall immediately provide the Department with the following information:

   (a) A description of and cause of noncompliance; and

   (b) The period of noncompliance, including dates and times; or, if not corrected, the anticipated time the noncompliance is expected to continue, and steps being taken to reduce, eliminate, and prevent recurrence of the noncompliance.

The permittee shall be responsible for any and all damages which may result and may be subject to enforcement action by the Department for penalties or for revocation of this permit.

GENERAL CONDITIONS:

9. In accepting this permit, the permittee understands and agrees that all records, notes, monitoring data and other information relating to the construction or operation of this permitted source which are submitted to the Department may be used by the Department as evidence in any enforcement case involving the permitted source arising under the Florida Statutes or Department rules, except where such use is prescribed by Section 403.111 and 403.73, F.S. Such evidence shall only be used to the extent it is consistent with the Florida Rules of Civil Procedure and appropriate evidentiary rules.

10. The permittee agrees to comply with changes in Department rules and Florida Statutes after a reasonable time for compliance; provided, however, the permittee does not waive any other rights granted by Florida Statutes or Department rules.

11. This permit is transferable only upon Department approval in accordance with Rule 17-4.120 and 17-30.300, F.A.C., as applicable. The permittee shall be liable for any non-compliance of the permitted activity until the transfer is approved by the Department.

12. This permit or a copy thereof shall be kept at the work site of the permitted activity.

13. This permit also constitutes:

( ) Determination of Best Available Control Technology (BACT)

( ) Determination of Prevention of Significant Deterioration (PSD)

( ) Certification of compliance with state Water Quality Standards (Section 401, PL 92-500)

( ) Compliance with New Source Performance Standards

The permittee shall comply with the following:

(a) Upon request, the permittee shall furnish all records and plans required under Department rules. During enforcement actions, the retention period for all records will be extended automatically unless otherwise stipulated by the Department.

(b) The permittee shall hold at the facility or other location designated by this permit records of all monitoring information (including all calibration and maintenance records and all original strip chart recordings for continuous monitoring instrumentation) required by the permit, copies of all reports required by this permit, and records of all data used to complete the application for this permit. These materials shall be retained at least three years from the date of the sample, measurement, report, or application unless otherwise specified by Department rule.

(c) Records of monitoring information shall include:

1. the date, exact place, and time of sampling or measurements;
2. the person responsible for performing the sampling or measurements;
3. the dates analyses were performed;
4. the person responsible for performing the analyses;
5. the analytical techniques or methods used;
6. the results of such analyses.

15. When requested by the Department, the permittee shall within a reasonable time furnish any information required by law which is needed to determine compliance with the permit. If the permittee becomes aware the relevant facts were not submitted or were incorrect in the permit application or in any report to the Department, such facts or information shall be corrected promptly.

PERMITTEE:
Ogden Martin Systems of Lake, Inc.

Attention: Dr. Gary Crane
Executive Vice President

I. D. Number:
Permit/Certification Number:
S035-187342
Date of Issue:
Expiration Date: 12/20/95

SPECIFIC CONDITIONS:

1. Drawings, plans, documents and specifications submitted by the permittee, not attached hereto, but remain on file at the Central District office, are made a part of this permit.

2. A copy of the permit, with a complete copy of the permit application and engineering drawings shall be kept on file at the facility for inspection and review upon request.

3. Signs indicating the name of the operating authority, traffic flow, hours of operation, charges for disposal and the types of wastes accepted shall be placed at all entrances to the site.

4. Access to the site shall be restricted by an effective barrier designed to prevent unauthorized entry and dumping.

5. The facility shall have litter control devices, dust controls, fire protection and fire-fighting facilities.

6. Safety devices shall be provided on equipment to shield and protect the operators from potential hazards during operation.

7. In the event of equipment malfunction, destruction, breakdown or other problems, the Department is to be immediately notified by the permittee as to the cause, what steps are being taken to correct the problem and prevent its recurrence as required by Rule 17-4.130, F.A.C.

8. The facility shall be staffed with sufficient personnel to properly operate and maintain the facility.

9. Communication facilities shall be available on-site.

10. Any liquids in the waste or clean up water from the tipping floor shall be mixed with and absorbed by the waste and incinerated. All stormwater that comes into contact with waste shall be collected and incinerated or treated to meet the requirements of Chapters 17-3 and 17-4, Florida Administrative Code, (F.A.C.).

11. Any operating characteristics or operating procedures which cause a public nuisance, such as excessive noise, odors, litter, etc. shall be satisfactorily resolved.

PERMITTEE:
Ogden Martin Systems of Lake, Inc.

Attention: Dr. Gary Crane
Executive Vice President

I. D. Number:
Permit/Certification Number:
S035-187342
Date of Issue:
Expiration Date: 12/20/95

SPECIFIC CONDITIONS:

12. The facility shall be operated so as to handle solid waste on a first-in, first-out basis. At no time shall any stored solid waste be allowed to remain unprocessed for more than 48 hours unless adequatge provisions are made to control flies, rodents and odors. (Rule 17-701.090(6), F.A.C.).

13. Due to continuous operations (24 hours per day, seven days per week) the facility shall be maintained during continuous operation, as necessary, to prevent fly, rodent and other vector problems. (Rule 17-701.090(8), F.A.C.).

14. The QA/QC program shall monitor several key aspects of the facility's operation and provide timely warning of unacceptable conditions of adverse trends such as:
    a) declining equipment performance or reliability,
    b) potential equipment failures,
    c) reoccurring problems or failures.

15. In the case of facility breakdown or natural disasters, the solid waste shall be taken to an approved landfill for disposal. (Rule 17-701.090(5), F.A.C.).

16. Lake County personnel will operate the scalehouse and shall be responsible for maintaining accurate records of all loads of waste delivered to the site, licensing and identification of the vehicles, types of waste delivered, and assessment and billing of tipping fees and other charges.

17. Performance records shall be kept as to the amount of solid waste incinerated and the rate of heat production (BTU's per hour). Also, records shall be kept as to the amount of electric power produced (Kilowatt hours) and the amount used in-house and the amount sold to the power company.

18. All ash residue shall be transported to and disposed of at a department approved (permitted) sanitary landfill having an in-place bottom liner and leachate collection system.

19. This permit does not preclude the requirements to obtain industrial waste and air permits.

20. The solid waste maximum processing rate for this source is 528 tons per day nominal, as stated in the permit application.

21. An operation permit renewal must be submitted at least 60 days prior to the expiration date of this permit. (Rule 17-4.090, F.A.C.)

PERMITTEE:
Ogden Martin Systems of Lake, Inc.

Attention: Dr. Gary Crane
Executive Vice President

I. D. Number:
Permit/Certification Number:
SO35-187342
Date of Issue:
Expiration Date: 12/20/95

SPECIFIC CONDITIONS:

ISSUED 2-8-91

STATE OF FLORIDA DEPARTMENT
OF ENVIRONMENTAL REGULATION

A. Alexander
Deputy Assistant Secretary
3319 Maguire Boulevard
Suite 232
Orlando, Florida 32803

ENVIRONMENTAL ASSESSMENT
Ropinirole (SK&F 101468) Tablets
NDA # 20-658

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SmithKline Beecham
Pharmaceuticals

COMPLIANCE STATEMENT

SmithKline Beecham(Manufacturing)Ltd. states that it is in compliance with, or on an enforceable schedule to be in compliance with,all emission requirements set forth in permits, consent decrees and administrative ordres applicable to the production of ROPINIROLE at it's facilities in Currabinny,Carrigaline,Co.Cork,Ireland.

F.A. Groeger 3/7/1995

Name : Dr.F.A.Groeger.
Title : Team Leader Quality Assurance/Regulatory Control.

Joe Foley 3/7/1995

Name : Mr.Joseph Foley.
Title : Process Team Leader.

Aqueous Discharge Limits for Cork, Ireland

Parameters	Units	Permit Limits
Total Ammonia (as N)	mg/L	50
Suspended Solids	mg/L	250
Zinc	mg/L	1.0
Copper	mg/L	0.5
COD	mg/L	4,000
BOD	mg/L	500
Nitrates (as N)	mg/L	15.0
Phosphate	mg/L	24.0
pH	-	6 - 9
Number of Toxicity Units [1]	TU	10.0
Organohalogens [2]	-	-

The volume of trade effluent discharged to the controlled waters shall not exceed 600 m^3 in any period of twenty-four hours.

The flow rate of trade effluent discharged to the controlled waters shall not exceed 151.2 m^3 per hour.

[1] ***The toxicity of the effluent shall be determined on an appropriate aquatic species. The number of toxic units (TU) = 100/96 hour LC50 in percentage vol/vol so that higher TU values reflect greater levels of toxicity.***

[2] ***Screening for a priority pollutant list is required (such as CPL 40, US EPA volatile and/or semi-volatile).***

Source: Integrated Pollution Control (IPC) licence
Issued Oct. 94 - Environmental Protection Act, 1992
Emission limits from 1st October 1995

ENVIRONMENTAL ASSESSMENT
Ropinirole (SK&F 101468) Tablets
NDA # 20-658

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SmithKline Beecham
Pharmaceuticals

14th March 1995

GENERAL COMPLIANCE STATEMENT

SMITHKLINE BEECHAM Pharmaceuticals states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Ropinerole at its facilities at Worthing.

pp. D. M. Yardley

Dr. D.W. Wiggins
Manager,
Safety & Environmental Control Dept.

pp. N. A. Ramsden 15/3/95

Mr. S. Ramsden
Projects Manager

000081

Aqueous Discharge Limits for Worthing, UK

Parameters	Units	Permit Limits
Suspended Solids	mg/L	5000
COD	mg/L	16,000
Acetone	mg/L	3000
Diisopropyl Ether	mg/L	2000
Ethyl Acetate	mg/L	1000
Isopropanol	mg/L	2000
Methylisobutylketone	mg/L	2000
Methylene Dichloride	mg/L	2000
Lead	µg/L	108
Zinc	µg/L	1120
Chromium	µg/L	236
Copper	µg/L	550

The volume of trade effluent discharged to the controlled waters shall not exceed 5000 m^3 in any period of twenty-four hours.

The rate of trade effluent discharged to the controlled waters shall not exceed 180.5 litres/sec.

Reference: National Rivers Authority/
Aqueous Discharge to Controlled Waters
Application #P1305A/S/CH/95
Effective through April 96

ENVIRONMENTAL ASSESSMENT
Ropinirole (SK&F 101468) Tablets
NDA # 20-658

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SB
SmithKline Beecham
Pharmaceuticals

GENERAL COMPLIANCE STATEMENT

SmithKline Beecham Pharmaceutical states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Ropinirole at its facilities in Crawley.

Name: John Elliot — Date: 22.6.95
Title: Director & Vice President Operations

Name: Dennis Hallifax — Date: 22/06/95
Title: Safety & Environmental Control Department

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AQUEOUS DISCHARGE LIMITS FOR CRAWLEY, UK

Parameters	Units	Permit Limits
Settleable Solids	mg/L	1000
COD	mg/L	2000
Ammoniacal Nitrogen (as N)	mg/L	35
Sulphate (as SO_4)	mg/L	1800
Available Chlorine (as Cl)	mg/L	50
Chromium (as Cr)	mg/L	3
Copper (as Cu)	mg/L	3
Lead (as Pb)	mg/L	3
Nickel (as Ni)	mg/L	2
Silver (as Ag)	mg/L	2
Zinc (as Zn)	mg/L	3
pH	SU	6 - 11
Temperature	°C (°F)	≤ 43.3 (110)

The maximum quantity of the trade effluent which may be discharged on any one day of twenty-four hours determined from midnight to midnight shall not exceed $250m^3$.

The maximum rate at which trade effluent may be discharged shall not exceed $25m^3$ per hour.

No condensing water shall be discharged.

Reference: Trade Effluent Consent
Trade Effluent Dept.
CROYDON
Consent No.: SYMCR005
Operates under The Water Industry Act 1991

ENVIRONMENTAL ASSESSMENT
Ropinirole (SK&F 101468) Tablets
NDA # 20-658

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MATERIAL SAFETY DATA SHEET

1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND OF THE COMPANY/UNDERTAKING

SUBSTANCE/PREPARATION:
ROPINIROLE
TRADENAMES/SYNONYMS:
4-[2-DIPROPYLAMINO)ETHYL]-1,3-DIHYDRO-2H-INDOL-2-ONE,MONOHYDROCHLORIDE * SK&F 101468-A * SKF-101468-A * ROPINIROLE * SK&F 101468-A * 101468-A (SK&F) * 101468-A (SKF)
CHEMICAL FAMILY:
Substituted indole.
MOLECULAR FORMULA:
C16-H24-N2-O . H-Cl
MOLECULAR WEIGHT:
296.84
COMPANY:
SMITHKLINE BEECHAM, CORPORATE ENVIRONMENT & SAFETY

U.S. OFFICE:	U.K. OFFICE:
709 SWEDELAND ROAD	NORFOLK HOUSE, DOWNSBROOK TRADING ESTATE
KING OF PRUSSIA, PA, 19406	SOUTHDOWNVIEW WAY, WORTHING
U.S.A.	WEST SUSSEX, BN14 8NQ, ENGLAND
PHONE NUMBERS:	
++1-610-270-7600	++44-(0)1903-822650

EMERGENCY AND AFTER HOURS CONTACT:
++1-612-221-3999, EXTENSION 221
++1-800-228-5635, EXTENSION 221 (Toll Free USA/Canada)

2.COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENTS	CAS REGISTRY NO	PERCENT
ROPINIROLE	91374-20-8	98

CONTAMINANTS:
No significant hazardous contaminants.

3. HAZARDS IDENTIFICATION

SKIN CONTACT:
Irritation can occur following direct contact with this material. Symptoms might include itching, redness, swelling or pain. Allergic skin reaction is not expected.
EYE CONTACT:
Irritation can occur following direct contact with this material. Symptoms might include redness, swelling, blurred vision or pain.
INHALATION:
Effects of breathing dust are not known. Symptoms of toxicity might include nausea, vomiting or reduced blood pressure when standing.
INGESTION:
Toxicity following ingestion can occur. Signs of toxicity might include nausea, vomiting or reduced blood pressure when standing.
CONDITIONS AGGRAVATED BY EXPOSURE:
Over exposure might impair milk production in breast feeding mothers, based on studies in animals.

4. FIRST-AID MEASURES

SKIN CONTACT:

Remove contaminated clothing and flush exposed area with water. Obtain medical assistance if irritation occurs.

NOTE TO PHYSICIAN:

None.

EYE CONTACT:

Flush eyes continuously with water for at least 15 minutes and obtain immediate medical attention.

NOTE TO PHYSICIAN:

Consider further flushing of eyes with large amounts of water or saline. Because of the possibility for permanent eye damage, refer all such cases to an ophthalmologist.

INHALATION:

Move exposed subject to fresh air. Seek medical assistance in case of known or possible overexposure to this material or with symptoms including chest pain, difficulty breathing, loss of consciousness or other adverse effects which may be delayed. IF BREATHING HAS STOPPED, START BASIC LIFE SUPPORT AND SEEK IMMEDIATE MEDICAL ATTENTION.

NOTE TO PHYSICIAN:

For combustion products, refer to section number 5.

INGESTION:

In the event of swallowing this material, seek medical assistance. Do not induce vomiting.

NOTE TO PHYSICIAN:

This material is a D2-dopamine agonist. In cases of overexposure, treatment should be supportive and symptomatic. A dopamine antagonist, such as domperidone, might be effective to block peripheral dopaminergic effects. This material is not corrosive.

ANTIDOTES:

None known.

5.FIRE-FIGHTING MEASURES

FIRE CONTROL:

Use water, carbon dioxide, foam or dry chemical extinguishers. Toxic or corrosive gases are expected from fires involving this material.

SPECIAL FIREFIGHTING PROCEDURES:

Since toxic, corrosive or flammable vapours might be evolved from fires involving this material, self contained breathing apparatus and full protective equipment are recommended for firefighters. Move containers from the fire area if possible without increased personal risk. If possible, contain and collect firefighting water for later disposal. Refer to MSDS Section 10 for expected thermal decomposition products.

6. ACCIDENTAL RELEASE MEASURES

SPILLS:

Remove or shut off all sources of ignition. Do not allow into drains. Instruct all personnel not involved in clean up operations to keep at a designated, safe distance. Wear protective clothing and equipment consistent with the degree of hazard. Carefully scoop up the spillage, avoid dust generation and place in a suitable, properly labeled container for recovery or disposal. Take care to avoid excessive dust during cleanup. Wash down spillage area with copious amounts of water. This must only be undertaken if waste water can be directed to an on-site waste water treatment system.

DECONTAMINATION PROCEDURES:

Water based detergents should be effective in clean-up and decontamination operations, but protective equipment must me worn to

avoid skin contact.

7. HANDLING AND STORAGE

HANDLING:

All plant, equipment and operators must be earthed (grounded) to ensure that no isolated conductors are present. Minimise the use of plastics when handling this material. This material is of low conductivity and coupled with its appreciable charge decay time might represent a source of electrostatic charge accumulation. Use only with adequate local exhaust ventilation or enclosure to routinely control airborne dust levels below published exposure limits.

STORAGE:

Avoid prolonged storage at elevated temperatures (greater than room temperature, approximately 20 degrees C). Keep in tightly closed containers or packages away from moisture.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

EXPOSURE CONTROLS:

ROPINIROLE:
SmithKline Beecham(PEL):
0.02 MG/M3 (8 HR TWA)
INDUSTRIAL HYGIENE METHOD:
SB/1127 analytical method.

PERSONAL PROTECTION:

RESPIRATORS:

If dust is present, a laboratory fume hood, local exhaust ventilation or an appropriate respirator should be used. The specific type used will be determined by air concentrations present. Follow local regulations for respirator use in the workplace.

GLOVES:

Wear impervious gloves.

EYE PROTECTION:

Wear chemical splash goggles when handling this material.

HYGIENE PRACTICES:

Wash hands and arms thoroughly after handling this material.
Clean up spills immediately.

OTHER PROTECTIVE EQUIPMENT:

Wear lab coat or other protective clothing with long sleeves.
An eye wash station should be available.

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE:

White to pale greenish yellow powder.

FLASH POINT:

Expected to be greater than 55 degrees C.

AUTOIGNITION TEMPERATURE:

Not determined.

LOWER EXPLOSIVE LIMIT

Not applicable for solids.

UPPER EXPLOSIVE LIMIT:

Not applicable for solids.

MELTING POINT:

Approximately 245 degrees C.

BOILING POINT:

Not applicable.

VAPOUR DENSITY:

Expected to be negligible.

VAPOUR PRESSURE:
Not determined.

EVAPORATION RATE:
Not determined.

VOLATILE COMPONENTS (%):
None expected.

VISCOSITY:
Not applicable for solids.

PH OF AQUEOUS SOLUTIONS:
Not determined.

RELATIVE DENSITY:
Not determined.

CONDUCTIVITY:
Not applicable for solids.

OCTANOL/WATER DISTRIBUTION COEFFICIENT:
Log P = 3.32 in phosphate buffer at pH 7.4.

DISSOCIATION CONSTANT (pKA):
9.5 for tertiary amine, 11.6 for indole nitrogen.

SOLUBILITY:
Soluble in water (133 mg/ml) and dilute hydrochloric acid.
Slightly soluble in ethyl alcohol.
Insoluble in methylene chloride.

OXYGEN BALANCE:
This material is considered to be of low energy hazard potential based on oxygen balance calculated as minus 234.

TRAIN FIRE TEST:
Since this material has not been train fire tested, it should be assumed to support combustion in bulk quantities.

DUST EXPLOSIVITY:
Classification: A
Minimum explosive concentration (grams/cubic metre): Not determined.
Minimum ignition temperature - cloud (degrees C): Not determined.
Minimum ignition temperature - layer (degrees C): Not determined.
Minimum oxygen concentration (% v/v): Not determined.
Explosion characteristics:
Pmax (bar): 6.9
dP/dT (bar/second): 875
Kst (bar metre/second): 237
St class: 2

DUST ELECTRICAL PROPERTIES:
Minimum ignition energy (mjoules): 10 to 15
Resistivity at ambient humidity (ohm meter): 2 x 10e12
Charge decay time at ambient humidity (seconds): 41
Resistivity at low humidity (ohm metre): 1 x 10e13
Charge decay time at low humidity (seconds): 4245

10. STABILITY AND REACTIVITY

CONDITIONS TO AVOID:
Avoid direct sunlight, conditions that might generate heat and dispersion as a dust cloud.

INCOMPATIBILITY:
Not determined.

STABILITY:
This material is expected to be stable.

THERMAL STABILITY:
Capillary tube test: Not determined.

Differential scanning calorimetry: Not determined.
Accelerating rate calorimeter: Not determined.

HAZARDOUS POLYMERIZATION:
Not expected to occur.

HAZARDOUS DECOMPOSITION PRODUCTS:
Not identified.

FIRE AND EXPLOSION HAZARDS:
Not identified. As with many organic dusts, explosions might result when excessive dust concentrations are present.

11. TOXICOLOGICAL INFORMATION

ORAL TOXICITY:
Oral LD50 values were 983 mg/kg in rats and 749 mg/kg in mice. This material exhibited moderate toxicity following a single, oral treatment.

INHALATION TOXICITY:
Not determined.

SKIN IRRITATION:
This material was classified as a mild irritant to rabbit skin. Redness occurred up to one day following direct application in rabbits for 4 hours. Skin appeared normal two days after treatment.

EYE IRRITATION:
This material was classified as a moderate irritant in rabbit eyes. Conjunctival redness, swelling and discharge, with iritis and corneal opacity occurred up to 3 days after direct application in rabbits. Eyes appeared normal 7 days after treatment. Water irrigation reduced irritation.

SENSITIZATION:
This material was classified as a non-sensitiser to guinea pig skin. No adverse skin reactions or irritation occurred in guinea pigs used to test for allergic reaction or sensitisation (maximisation test).

MUTAGENICITY:
This material was not mutagenic in bacteria (Ames test) or other laboratory tests (in vivo cytogentics, mouse lymphoma test and mouse micronucleus test).

CARCINOGENICITY:
This material is listed as an animal carcinogen according to SB criteria (category 2). It is not listed as a carcinogen by IARC, NTP or US OSHA.

REPRODUCTIVE EFFECTS:
No teratogenic effects (birth defects) occurred in rabbits. In studies with rats, teratogenic effects occurred at high dose levels significantly higher than human clinical doses. After birth, decreased pup growth also occurred apparently related to impaired maternal lactation.

OTHER EFFECTS:
This material is a dopamine D2 receptor agonist developed for use in the treatment of Parkinson's Disease.

12. ECOLOGICAL INFORMATION

ACUTE AQUATIC EFFECTS:
Not determined.

BIODEGRADATION:
Expected to be fairly biodegradable.

ACTIVATED SLUDGE RESPIRATION INHIBITION (OECD 209 PROTOCOL):
Not determined.

SOIL ADSORPTION:

Not determined.
OTHER EFFECTS:
Not determined.

13. DISPOSAL CONSIDERATIONS

Collect for recycling or recovery, if possible. Dispose of material on site in a licensed chemical incinerator, if allowed by the incinerator license or permit. If no on-site incinerator is available, dispose of material in a licensed commercial chemical incinerator.

14. TRANSPORT INFORMATION

Proper Shipping Name: Not applicable.
Technical Name: Not applicable.
UN Number: Not applicable.
FOR AIR TRANSPORT (IATA REQUIREMENTS):
Non-hazardous according to IATA requirements.
FOR MARITIME TRANSPORT (IMDG REQUIREMENTS):
Non-hazardous according to IMDG requirements.
FOR UNITED STATES GROUND TRANSPORT (DOT REQUIREMENTS):
Non-hazardous according to US DOT requirements.
FOR EUROPEAN GROUND TRANSPORT (ADR/RID REQUIREMENTS):
Non-hazardous according to ADR/RID requirements.

15. REGULATORY INFORMATION

EUROPEAN UNION CLASSIFICATION AND LABELLING REQUIREMENTS:

FIRE CLASSIFICATION
Not classified as a significant fire hazard
HEALTH CLASSIFICATION
Harmful Irritant

ENVIRONMENTAL CLASSIFICATION
(Leave blank)
RISK PHRASES:
Harmful if swallowed. (R22)
Irritating to eyes.(R36)
SAFETY PHRASES:
Avoid contact with eyes. (S25)
In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. (S26)
Wear suitable protective clothing. (S36)
SYMBOL:
Saint Andrew's Cross.(Xn) & Saint Andrew's Cross.(Xi)

16. OTHER INFORMATION

HAZARD LABELLING:
**** NOT CLASSIFIED AS A SIGNIFICANT FIRE HAZARD ****
**** HARMFUL & IRRITANT ****
**** CAUTION - ENVIRONMENTAL HAZARD NOT FULLY IDENTIFIED ****
** HARMFUL IF SWALLOWED.
** IRRITATING TO EYES.
** AVOID CONTACT WITH EYES.

** IN CASE OF CONTACT WITH EYES, RINSE IMMEDIATELY WITH PLENTY OF WATER AND SEEK MEDICAL ADVICE.
** WEAR SUITABLE PROTECTIVE CLOTHING.
** TARGET ORGAN- NO SPECIFIC TARGET ORGAN EFFECTS KNOWN.
** SYMBOL: SAINT ANDREW'S CROSS.(XN) & SAINT ANDREW'S CROSS.(XI)

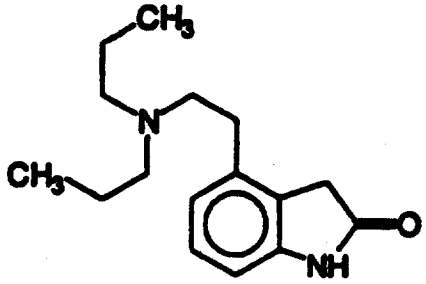
REFERENCES:
SB HAZARD DETERMINATION

OTHER INFORMATION:
IF HMIS RATINGS ARE USED AT YOUR SITE, USE THE FOLLOWING:
HEALTH = 1 FIRE= 1 REACTIVITY = 0

ROPINEROLE (SK&F 101468)

SMITHKLINE BEECHAM ENVIRONMENTAL RESEARCH LABORATORY
SUMMARY OF ENVIRONMENTAL DATA
CURRENT AS OF 06 JANUARY 1997

STRUCTURE $C_{16}H_{24}N_2O$



SMILES - O=C(Nc(c1c(cc2)CCN(CCC)CCC)c2)C1

MOLECULAR WEIGHT - free base 260.38, HCl salt 296.84 g/mol (IND 31,713 CMC)

CAS # - 91374-20-8

ENVIRONMENTAL FATE

Solubility (IND 31,713 CMC)

Solvent	Solubility (mg/L)
Water (pH ?)	133000
0.1 M HCl	86900
0.1 N NaOH	>3700
EtOH	4200
methylene chloride	300

pK_a

(Physicochemical Characterization of SK&F 101468-A, *SK&F Report CP002BA*)
pK_1=9.5 (tertiary amine)
pK_2=11.6 (indole nitrogen)

(Further Physicochemical Properties of SK&F 101468A, *SK&F Report CW002BA*)
pK_1 = 9.68 (tertiary amine)
pK_2 = 12.43 (indole nitrogen)

Activated Sludge Adsorption (ERL study S94015P, lyophilized sludge solids)
Preliminary Kinetics Experiment (A)
- time to equilibrium < 2.4 hours
- mean K_d after 2.4 hours = 55.7 ± 12.6 (SD) mL/g (log K_d=1.75)

Amended page

Definitive Isotherm Determination (B)

- Freundlich isotherm constant, log K = 1.92 (K = 83.2)
- isotherm slope, 1/n = 0.967 (a 1/n value of 1.00 indicates K_d is independant of test chemical concentration)
- isotherm linear correlation coefficient, R^2 = 0.998

Octanol/Water Partition Coefficient

(Physicochemical Characterization of SK&F 101468A, *SK&F Report CP002BA*)
log P_{ow} at pH 7.4 = 3.32 (by HPLC method)

(Further Physicochemical Properties of SK&F 101468A, *SK&F Report CW002BA*)
log D_{ow} at pH 8.43=2.33 (by shake flask method)

UV/vis Spectrum

(Physicochemical Characterization of SK&F 101468-A, *SK&F Report CP 002 BA*)
pH 3
10 µg fb/mL (3.84×10^{-5} M)
λ_{max}=249 nm
ε_λ=31.07 L/g-cm (9.22×10^3 M^{-1}-cm^{-1})
UV/vis cutoff ~300 nm

Direct Photolysis (ERL study S94013P)

Not experimentally determined. Direct photolysis kinetics estimated using the procedures of Leifer (1988, *The Kinetics of Environmental Aquatic Photochemistry: Theory and Practice*, American Chemical Society, Washington, D.C., 304 pps.). Assumed ϕ_d = 0.05.

	summer irradiance		winter irradiance	
pH	k_{dE} (day^{-1})	$t_{1/2}$ (days)	k_{dE} (day^{-1})	$t_{1/2}$ (days)
5	2.68E-3	259	1.16E-4	5970
7	1.60E-3	433	5.05E-5	13700
9	2.36E-3	294	8.75E-5	7920

Henry's Law Constant (ERL study S95002P)

experimental $H_L = 5.69 \times 10^{-7}$ m^3-atm/mol,
slope of volatilization curve not significantly different from zero at α=0.05

ENVIRONMENTAL EFFECTS

Bluegill sunfish 96 hour acute (Wildlife International. Ltd. study 374A-101)
EC50 = 11 mg/L
NOEC = 3.7 mg/L

***Daphnia magna* 48 hour acute (ERL Study)**
EC50 = 41.1 mg/L[a]
NOEC = 4.4 mg/L[a]

[a] preliminary data

OTHER

Stability - (Physicochemical Characterization of SK&F 101468-A, *SK&F Report CP 002 BA*) The neat drug substance was stable for 5 weeks from 30 to 60 °C at up to 75% relative humidity in the dark. When exposed to 600-700 foot-candles of illumination from a sunlamp, ~5% degradation was observed over 5 weeks.

In aqueous solution under darkened storage conditions, drug substance stability appears to be inversely related to pH:

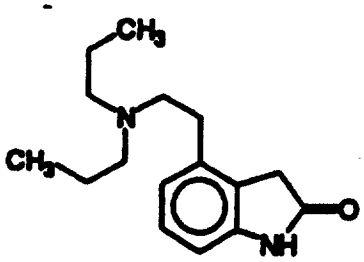
Degradation of 2 mg/mL Solutions of SK&F 101468 Stored at 85 °C for 4 Days:

Initial pH	% of Initial Remaining
3.00	101.5
4.28	92.9
5.45	69.5
6.30	40.9
7.51	11.3
8.98	5.7

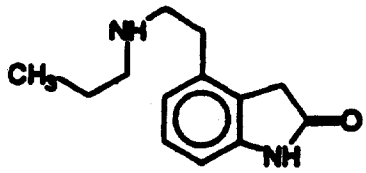
In summary, aqueous solutions of SK&F 101468 should be prepared at low pH and stored in the dark at low temperature to maximize drug substance stability.

Metabolism - Metabolism of ^{14}C-SK&F 101468 was determined in 4 human subjects by two doses separated by at least 28 days. Excretion of ^{14}C was rapid and essentially complete following both intravenous and oral doses. Most of ^{14}C activity was excreted in urine. Metabolism was extensive (Figure 1).

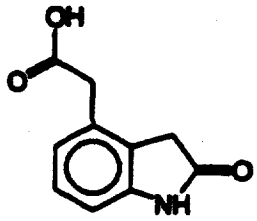
Figure 1. Human Metabolites of 14C-SK&F 101468 (≥ 10%)



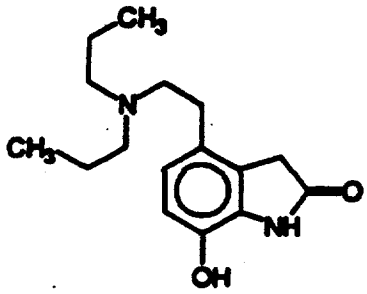
SK&F 101468 (parent) (~10%)



SK&F 104557 (~32-45%)



SK&F 097930 (~10%)



SK&F 089124 (~10%)

ENVIRONMENTAL ASSESSMENT
Ropinirole (SK&F 101468) Tablets
NDA # 20-658

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ENVIRONMENTAL ASSESSMENT

Ropinirole (SK&F 101468) Tablets

NDA # 20-658

STATUTORY INSTRUMENTS FOR THE UNITED KINGDOM APPLICABLE TO THE PRODUCTION OF ROPINIROLE

WASTE ON LAND

PUBLIC HEALTH (SCOTLAND) ACT 1897
PUBLIC HEALTH ACT 1936
PUBLIC HEALTH ACT 1961
PUBLIC HEALTH (RECURRING NUISANCES) ACT 1969
CONTROL OF POLLUTION ACT 1974
ENVIRONMENTAL PROTECTION ACT 1990
CIVIC GOVERNMENT (SCOTLAND) ACT 1982
CONTROL OF POLLUTION ACT 1974, THE COLLECTION AND DISPOSAL OF WASTE REGULATIONS
CONTROL OF POLLUTION (AMENDMENT) ACT 1989
CONTROL OF POLLUTION (SPECIAL WASTE) REGULATIONS 1980

POLLUTION OF INLAND WATERS

PUBLIC HEALTH ACT 1936
PUBLIC HEALTH (DRAINING OF TRADE PREMISES) ACT 1937
SEWERAGE (SCOTLAND) ACT 1968
CONTROL OF POLLUTION ACT 1974
ENVIRONMENTAL PROTECTION ACT 1990
RIVERS (PREVENTIONS OF POLLUTION) (SCOTLAND) ACT 1951
RIVERS (PREVENTIONS OF POLLUTION) (SCOTLAND) ACT 1965
RIVERS (PREVENTIONS OF POLLUTION) (SCOTLAND) ACT 1964
WATER RESOURCES ACT 1963
COUNTRYSIDE ACT 1968
WATER (SCOTLAND) ACT 1980
DRAINAGE ACT 1976
WATER ACT 1989
CONTROL OF POLLUTION (CONSENTS FOR DISCHARGES, ETC.) (SECRETARY OF STATE FUNCTIONS) REGULATIONS 1989
TRADE EFFLUENTS (PRESCRIBED PROCESSES AND SUBSTANCES) REGULATIONS 1989
CONTROL OF POLLUTION (REGISTERS) REGULATIONS 1989

ENVIRONMENTAL ASSESSMENT

Ropinirole (SK&F 101468) Tablets

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POLLUTION OF THE SEA

FOOD AND ENVIRONMENT PROTECTION ACT 1985

ATMOSPHERIC POLLUTION

ALKALI, &c. WORKS REGULATIONS ACT, 1906
CLEAN AIR ACT 1956
CLEAN AIR ACT 1968
HEALTH AND SAFETY AT WORK, ETC. ACT 1974
HIGHWAYS ACT 1980
CLEAN AIR (HEIGHT OF CHIMNEYS EXEMPTION) (SCOTLAND) REGULATIONS 1969
BUILDING STANDARDS (SCOTLAND) REGULATIONS 1981
CONTROL OF ATMOSPHERIC POLLUTION (EXEMPTED PREMISES) (SCOTLAND) REGULATIONS 1982
CONTROL OF ATMOSPHERIC POLLUTION (APPEALS) (SCOTLAND) REGULATIONS 1982
AIR QUALITY STANDARDS REGULATIONS 1989
CONTROL OF INDUSTRIAL AIR POLLUTION (REGISTRATION OF WORKS) REGULATIONS 1989
CONTROL OF ASBESTOS IN THE AIR REGULATIONS 1990

NOISE POLLUTION

PUBLIC HEALTH ACT 1936 STATUTORY NUISANCE
CONTROL OF POLLUTION ACT 1974
ENVIRONMENTAL PROTECTION ACT 1990
CONTROL OF NOISE (MEASUREMENT AND REGISTERS) REGULATIONS 1976
CONTROL OF NOISE (APPEALS) (SCOTLAND) REGULATIONS 1983
CONTROL OF NOISE (CODES OF PRACTICE FOR CONSTRUCTION AND OPEN SPACES)- 1985